



# SURGERY

A Monthly Journal Devoted to the Art  
and Science of Surgery

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# SURGERY

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## Original Communications

### SYMPATHECTOMY IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

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(From the Department of Surgery, The Johns Hopkins University School of Medicine)

DISORDERS of the peripheral circulation offer a particular challenge to the medical profession because of their common occurrence and their disabling character. Their treatment, largely neglected in the past, has been the subject of intensive study in recent years. Although sympathectomy is still a controversial issue, there is no doubt in my mind that it is one of the most valuable aids in the treatment of peripheral vascular disease. It is my purpose to discuss the importance of the study of cases in an attempt to evaluate the possible benefit which may be derived from sympathectomy, to describe the technique employed in sympathetic denervation of the upper end of the lower extremities, and to present the results of such operations in a series of cases which I have studied. It is not within the province of this communication to discuss the diagnosis of peripheral vascular disease. As Homans<sup>1</sup> has pointed out in his excellent monograph, the sorting out of the various disorders of the peripheral circulation is not a particularly difficult task and no elaborate diagnostic equipment is necessary.

#### THE STUDY OF CASES

Sympathectomy may be helpful in three ways: It may increase circulation through the elimination of vascular spasm; it may increase the warmth of the affected part by causing cessation of sweating and reduction of heat loss; and it may give relief from pain. Before a patient is subjected to this operation it should be determined whether he will be likely to benefit by it and to what extent. The method employed in this determination is best illustrated by a study of patients with arterial circulatory deficiency, the largest group to whom sympathectomy is applicable. Diminution in peripheral arterial circulation may be due to occlusion of vessels, to vasospasm, or to a combination of the two.

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It is essential to determine in which category any given case belongs. Blood flow cannot be restored through obliterated arteries, but vascular spasm can be effectively released. From history and ordinary examination, from the presence or absence of the major pulsations, from the character of the arteries on palpation and on x-ray examination, from the color changes in the extremity with alteration of position and after release of a constricting tourniquet, from the stability or lability of warmth of the affected part, much can be learned as to the degree to which vascular spasm contributes to the arterial circulatory deficiency. It is, however, important to measure the degree of vasospasm as accurately as possible.

The method employed is observation of the skin temperature of the affected part before and during inhibition of sympathetic vasoconstrictor impulses. Observations of thermal changes may be supplemented by oscillometry, various types of digital plethysmography, or plethysmographic study of muscle blood flow. The subject is first placed with the limbs exposed in a cool room, preferably one constantly maintained at 20° C. The rate and degree of cooling are noted by frequent measurements with a thermocouple. The digits often cool to room temperature, and they may become even cooler if there is sufficient loss of heat by evaporation from an actively sweating extremity. This phenomenon is commoner in the vasospastic diseases but may also be noted in obliterative arterial disease. After the skin temperature has become stabilized, sympathetic vasoconstrictor impulses may be eliminated in a number of ways. A simple and useful test is the thorough warming of the body, which may be done by a hot air cabinet,<sup>2</sup> by wrapping in blankets and a rubber sheet<sup>3</sup> or by the use of electric pads, and by diathermy over the lumbosacral area.<sup>4</sup> A similarly useful test is the immersion of the other extremities in warm water.<sup>5</sup> I occasionally employ such body-warming tests, particularly in order to study vasospasm both in upper and lower extremities at the same time. If good vasodilatation does not occur it is my feeling that some other test should be used as a supplementary check. Spinal anesthesia may be used in good-risk patients who are being hospitalized<sup>6, 7</sup> and is especially valuable when both lower extremities must be investigated. General anesthesia can also be used,<sup>6</sup> but is ordinarily not advisable unless anesthesia is necessary for some other purpose.

A simple and effective test which can be carried out without special equipment and on ambulatory patients is the study of thermal changes in the distribution of a peripheral nerve which has been anesthetized with procaine.<sup>8</sup> I frequently employ posterior tibial nerve block for study of the feet and ulnar nerve block for study of the hands. Peripheral nerve block should not be carried out if there is infection or gangrene in the region where the injection must be made. The direct infiltration of the sympathetic nerves with procaine<sup>9</sup> is in many respects the ideal test, for it has the advantage over all the other methods

in permitting the study of the effect on pain of interruption of the sympathetic nerves. For this reason it should be used, in my opinion, whenever pain is present. One can study not only the effect on resting pain but also on intermittent claudication. The technique of injection is not difficult; it is not a painful procedure, it may be carried out on ambulatory patients, and if small doses of 0.5 per cent procaine with adrenalin are used and care is taken to avoid injection into the blood stream, pleural sac, and subarachnoid space, it is a safe procedure.<sup>9</sup> The accuracy of the injection of the upper dorsal sympathetics is attested by the presence of a Horner's syndrome. If doubt exists as to the accuracy of lumbar sympathetic injection, the matter can be checked by cutaneous resistance studies.<sup>10</sup>

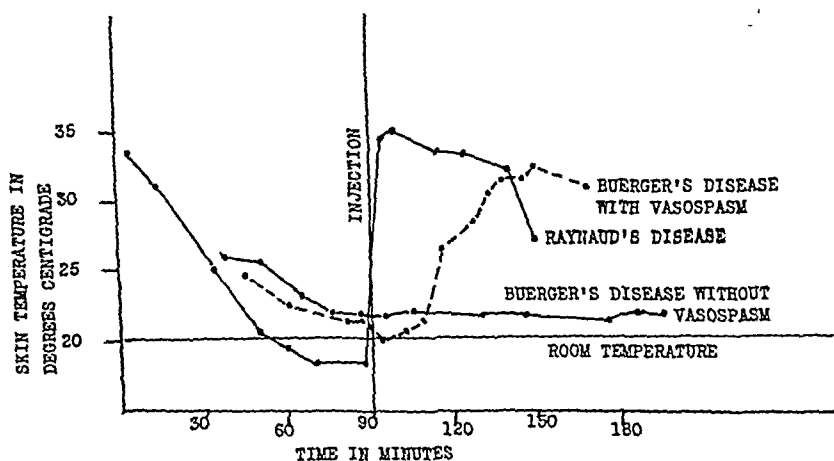


Fig. 1.—Skin temperature changes in a single digit before and after inhibition of vasoconstrictor impulses by sympathetic or peripheral nerve block in a case of Raynaud's disease and in two cases of Buerger's disease.

If more than one extremity is affected the element of vasospasm should be studied in the extremity with the most severe damage. One can assume then that the capacity of the vascular bed in the other extremities to dilate is somewhat better than or at least as good as in the extremity studied. Observation of the skin temperature in the contralateral limb serves as a control during study of thermal changes in the limb being investigated during inhibition of vasoconstrictor impulses. In Fig. 1 are charted examples of thermal changes after sympathetic or peripheral nerve block in cases of pure vasospastic disease, obliterative arterial disease with considerable vasospasm, and obliterative disease with little or no vasospasm. Misleading information may be obtained if the skin temperature of only a single digit is followed as was commonly done by the early workers. Fig. 2 illustrates that rise of temperature may be negligible in one digit but good in others.

Essentially the same sort of study is carried out in other types of peripheral vascular disease in which sympathectomy is under consideration. In cases of causalgia one is particularly interested in the

question of relief of pain. In postphlebotic states one should try to ascertain whether there exists demonstrable evidence of vasospasm in the affected extremity. Sometimes this is evident from skin temperature studies. Sometimes there is hyperhydrosis. In some instances I

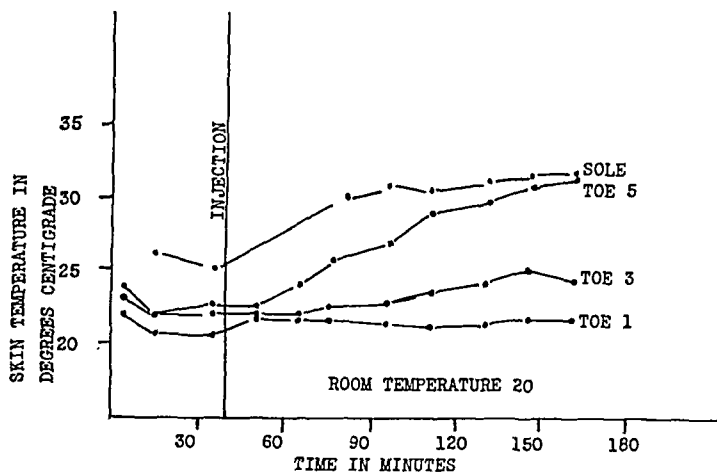


Fig. 2.—Skin temperature changes in a patient with Buerger's disease before and after posterior tibial nerve block. The variation in the response in different toes is illustrated.

have found an area of abnormally low cutaneous resistance and sometimes an area of hyperhydrosis in the region above the internal malleolus where pigmentation and ulceration so frequently occur, an observation which may be indicative of a localized region of vasospasm.

#### THE TECHNIQUE OF SYMPATHECTOMY

A preganglionic type of operation is employed for dorsal as well as lumbar sympathetic denervation. Regardless of whether those are correct who feel that the chief advantage of a preganglionic operation is in a lesser tendency toward subsequent development of adrenalin sensitivity,<sup>11</sup> this operation seems to give better results than a post-ganglionic operation. For lumbar sympathectomy I use with slight modification the muscle-splitting extraperitoneal operation which is commonly employed.<sup>12,13</sup> This approach is easier, permits a more adequate exposure of the entire lumbar ganglionated chain, and carries with it far less risk than the transperitoneal operation.

Spinal anesthesia is used as a routine procedure unless specifically contraindicated. The patient is placed on his back with the side to be operated upon slightly elevated by a sandbag under the corresponding hip. The skin incision extends from the tip of the twelfth rib to a point about midway between the umbilicus and the anterior superior spine of the ilium (Fig. 3). The external oblique muscle and fascia are divided in the line of the fibers and dissected back so as to expose adequately the internal oblique muscle; this is then divided in the direction of its fibers, the incision being placed so as to point to the

second lumbar vertebra or about three inches above the umbilicus. The incision is carried as far as the border of the rectus sheath. Care is taken to avoid injury to the underlying intercostal nerve. The transversalis muscle and fascia are similarly divided. Blunt dissection with the fingers is now carried down in the extraperitoneal space until

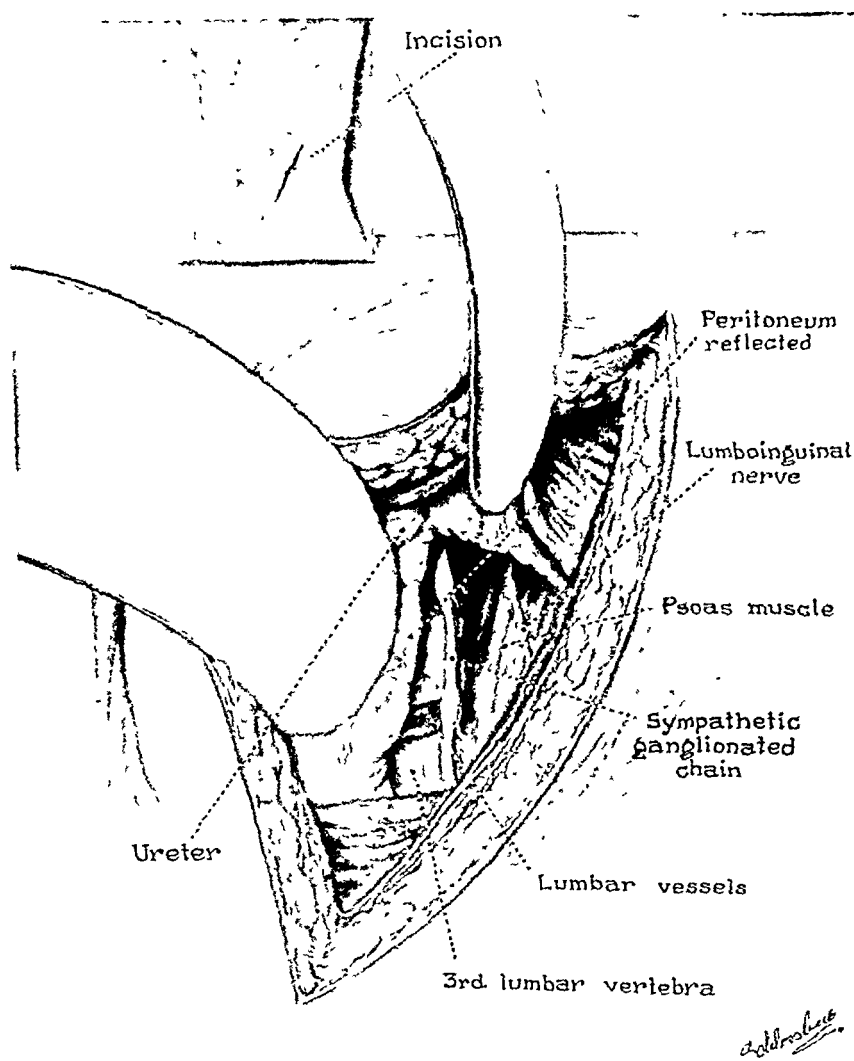


Fig 3.—Lumbar sympathectomy.

the iliopsoas muscle is felt, then anteriorly over the muscle until the fingers palpate the body of the vertebra. One can readily identify the ganglionated sympathetic chain with the finger tips and can then proceed to dissect gently up and down along the course of the chain. A broad Deaver retractor is introduced and retracted mesially, ex-

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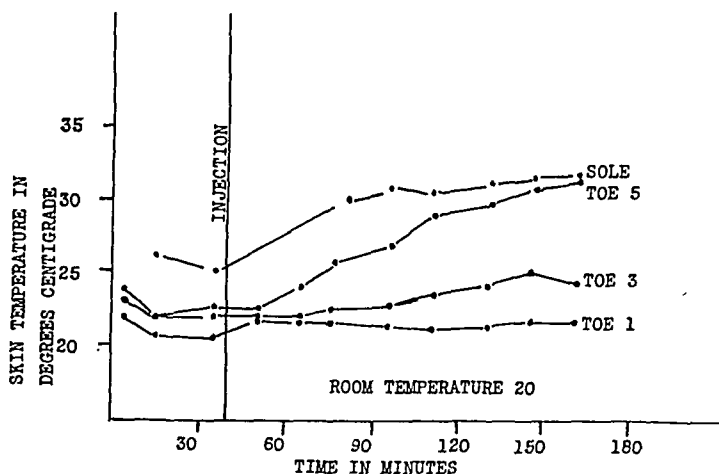


Fig. 2.—Skin temperature changes in a patient with Buerger's disease before and after posterior tibial nerve block. The variation in the response in different toes is illustrated.

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subcuticular sutures of fine silk. The operation can usually be completed in twenty to forty minutes.

The operation used for denervation of the upper extremities is essentially the upper dorsal sympathectomy proposed by Smithwick.<sup>11</sup> It is the same type of operation which Telford performs through an anterior incision.<sup>14</sup> A modified muscle-splitting posterior approach is used (Fig. 4). The patient is placed prone on the table with a sandbag

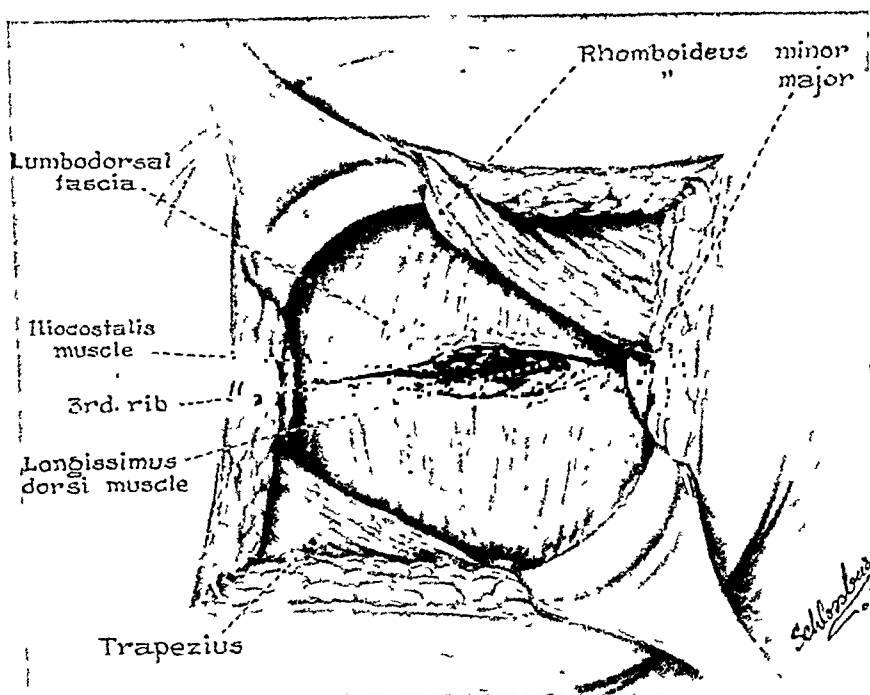


Fig 4B—Dorsal sympathectomy with incision through lumbodorsal fascia

under the sternum, one arm lying alongside the trunk, the other forward along the head. The patient is anesthetized with sodium pentothal given intravenously. In my opinion this anesthetic is far superior to inhalation anesthetic with or without an intratracheal catheter. An incision 7 or 8 cm long is made from the first thoracic spinous process to the spine of the scapula. The trapezius muscle is incised in the line of its fibers, thus exposing the rhomboid muscles, which are divided in the line of the fibers. The ribs are identified and an incision is made through the lumbodorsal fascia over the third rib. The mesial portion of this incision is continued through the iliocostalis cervicis. Sometimes a few of the lateral fibers of the longissimus dorsi are divided. The periosteum of the rib is incised and the inner 3 cm of the rib are removed, care being taken to avoid opening the pleura. The pleura and the endothoracic fascia are pushed back gently from the second



posing the vertebrae, the aorta or vena cava, and the sympathetic chain. The ureter lies in the extraperitoneal fatty tissue, which is held out of the field by the retractor. The lumbo-inguinal nerve is seen lying on the iliopsoas muscle and should not be injured. A small Deaver retractor is placed in the upper or lower end of the wound as needed to

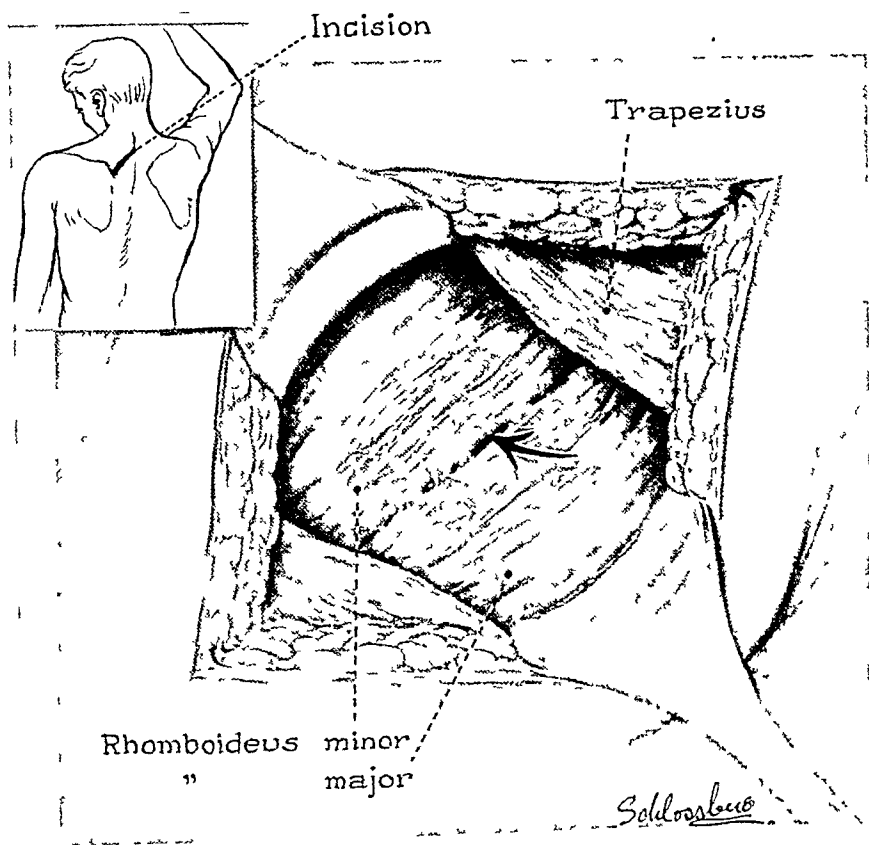


Fig 4A —Dorsal sympathectomy, showing position of the patient and line of incision. The trapezius has been incised and the arrow indicates point of separation of the rhomboids

bring the upper or lower ganglia into view. A silk traction suture slipped around the chain by means of an aneurysm needle aids in dissection. The ganglia are identified. The fourth lies proximal to the promontory of the sacrum. The rami of the third and fourth ganglia generally point caudally and those of the second point cephalad. In females the first, second, and third ganglia and the intervening chain are resected. In males the second and third or the second, third, and fourth are resected, since removal of the first ganglion interferes with ejaculation. Ordinarily no bleeding occurs. The transversalis, the internal, and the external oblique muscles and fascia are closed with interrupted sutures of fine silk, and the skin is closed with interrupted

extradural; but Smithwick has suggested intradural division as an additional safeguard against regeneration, and I believe this procedure is preferable. The freed spinal ganglion is picked up and the rami to the sympathetic ganglion are divided. The intercostal nerve is now divided so that the excised specimen consists of the inner inch of the nerve with its ganglion and dorsal and anterior roots.

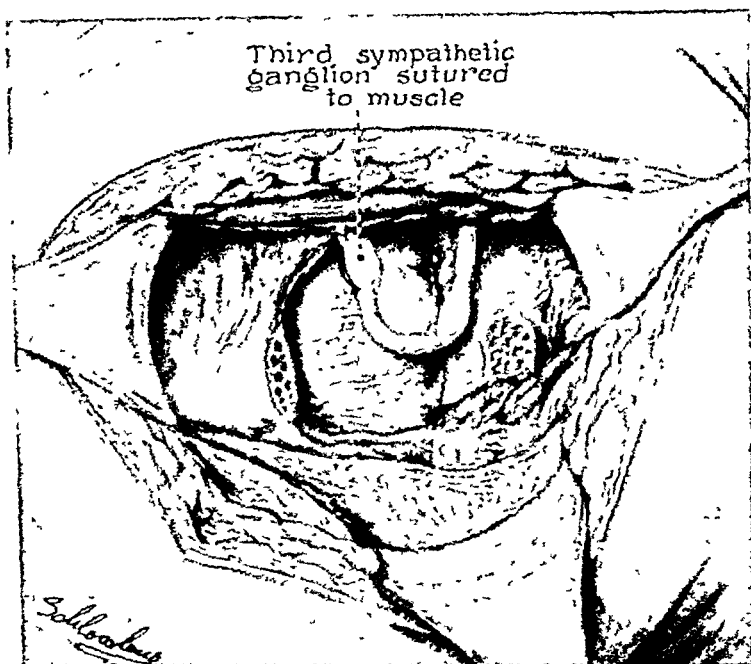


FIG. 4D.—Dorsal sympathectomy. The sympathetic chain is sutured to the muscle.

After this procedure has been carried out with both second and third nerves the sympathetic chain is divided caudad to the third ganglion and the freed chain and decentralized second and third ganglia are brought up into the wound and sutured to the muscle. A few interrupted sutures of fine silk approximate the iliocostalis muscle, the rhomboids, and the trapezius. The skin is closed with subcuticular sutures of silk. It is my custom to place in the extrapleural space before closure of the wound about 4 Gm. of sulfanilamide powder. Once in a while a pleural tear will occur, though this can usually be avoided by care in freeing and removing the rib and in stripping back the endothoracic fascia. When it occurs the lung is fully expanded by positive pressure before the wound is closed, and no harm results.

Patients recover quickly from both the lumbar and the dorsal operation. They are ordinarily able to sit up in a chair within a few days and may be subjected to a second operation in from four to seven days. Immediately after operation the denervated extremity is dry and warm to its maximum extent. Cutaneous resistance is high. A curious

and fourth ribs and from the vertebral body. The tip of the transverse process and the remaining head and neck of the rib are removed. The second and third intercostal nerves are identified and dissected free down to the dorsal root ganglia. Just beneath are the second and third sympathetic ganglia. A nerve hook is introduced between the anterior and posterior roots and by retraction these roots are brought into view. The dorsal root is divided and then the anterior root is divided either extradurally or intradurally. In many of my cases the division was

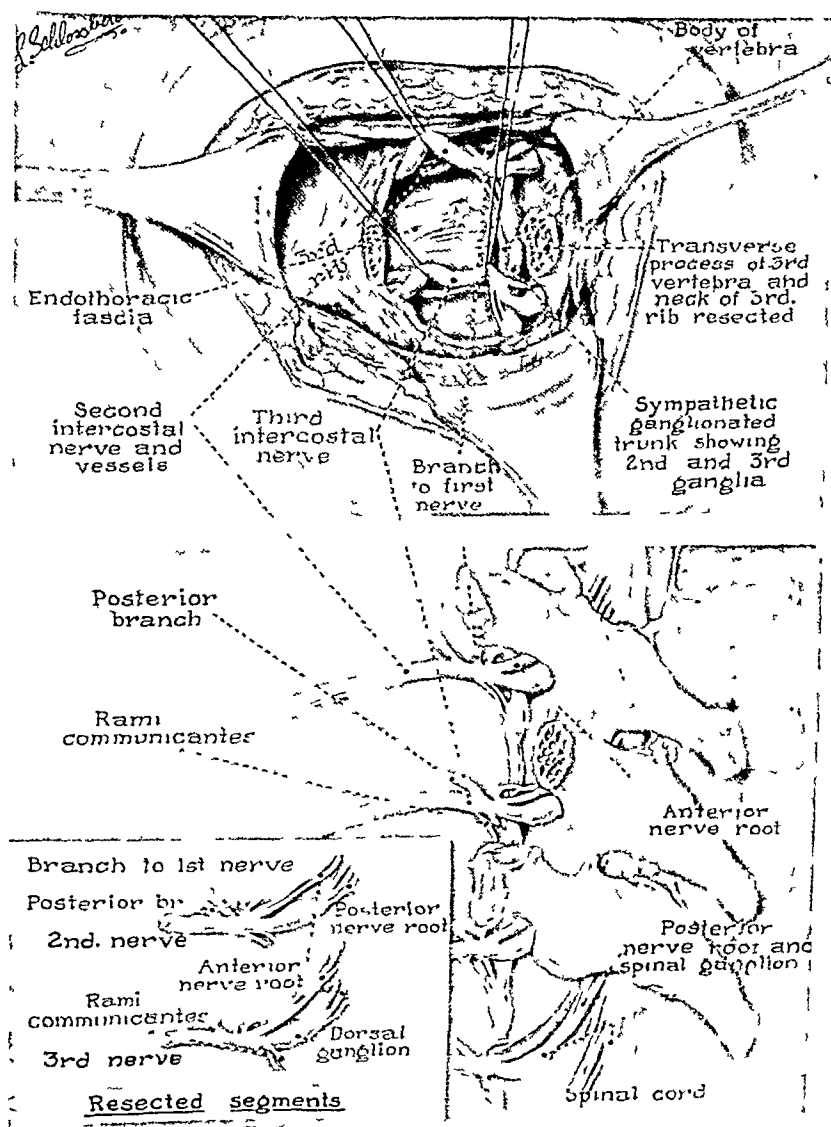


Fig 40.—Dorsal sympathectomy. The third rib and tip of transverse process have been resected, there is exposure of the intercostal nerves anterior and posterior roots, and the sympathetic chain.

The young woman in whom there was purpura limited to the vasospastic lower limbs, and with negative hematologic studies and negative tourniquet test in the arms, showed little or no improvement in the purpura although this is well controlled with elastic stockings, and her coldness and numbness have disappeared. The patient with causalgia has had no further pain. One patient included in this group was a

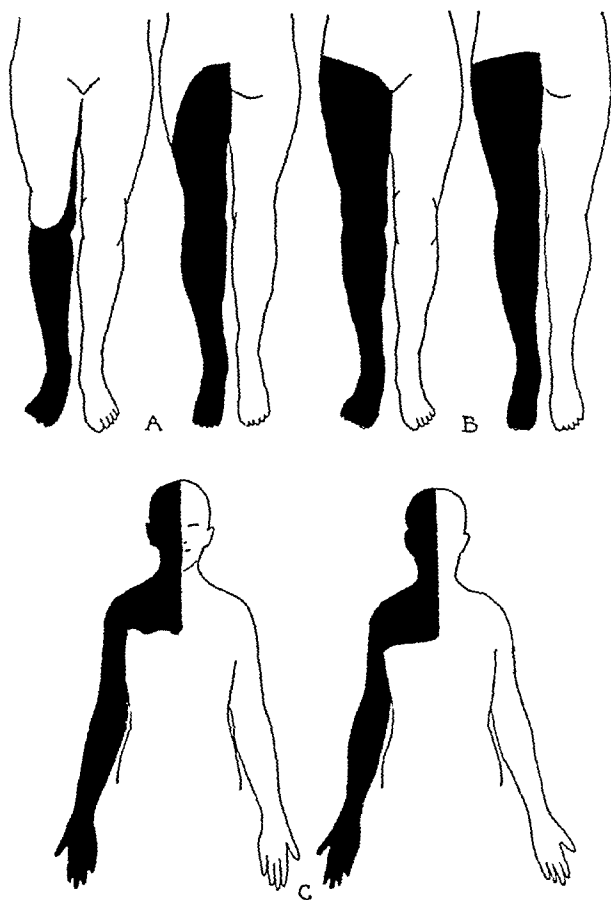


Fig. 5.—Showing the area denervated by removal of the second and third lumbar ganglia (A), by removal of the first, second, and third ganglia (B), and by dorsal sympathectomy (C), the areas inked in do not sweat on the Minor test and have abnormally high cutaneous resistance.

young man with elephantiasis in whom hyperhydrosis was so great that maceration of the skin occurred. It was felt hazardous to proceed with the plastic operation for elephantiasis until the hyperhydrosis had been corrected by sympathectomy.<sup>10</sup>

*Results of Sympathectomy for Phlebitic Sequelae and Chronic Leg Ulcers.*—Fourteen lower limbs have been sympathectomized in thirteen patients who suffered from phlebitic sequelae or chronic leg ulcers. Ten of the patients had had femoro-iliac thrombophlebitis; six of these

phenomenon occurs on about the fourth, fifth, or sixth day. The hand or foot cools, cutaneous resistance falls somewhat, and sweating may even occur. The degree of this change is variable, and it is much more noticeable in the hands than in the feet. No entirely satisfactory explanation for this phenomenon has been found. It may be due to vasoconstrictor impulses arising in the decentralized sympathetics associated with degeneration of fibers. At any rate, within a few days the skin temperature again rises as does the cutaneous resistance, and sweating is impossible. This state of affairs continues indefinitely. Should degeneration occur at some future date, evidence of vasoconstriction would return. In the present series there has been no evidence of regeneration following either dorsal or lumbar sympathectomy. The area which has been denervated may be outlined by the Minor sweating test or by mapping out of the area of high resistance to the passage of a small electrical current.<sup>15</sup> The areas denervated by removal of the second and third lumbar ganglia, by removal of the first, second, and third lumbar ganglia, and by the dorsal sympathectomy are illustrated in Fig. 5.

#### RESULTS OF SYMPATHECTOMY

The present series consists of 83 sympathectomies performed upon 54 patients in the Johns Hopkins Hospital since November, 1939. Included are only those cases studied by me. The operations have been performed either by me or by the resident staff under my direction.

*Results of Sympathectomy in Vasospastic Disease.*—Twenty-six sympathectomies have been performed upon thirteen patients with vasospastic disease (Table I). Seventeen upper and nine lower extremities were denervated. Nine of the patients were females, four were males. Eight of them suffered from the common type of Raynaud's disease. Four additional patients had a Raynaud-like syndrome: One was associated with severe causalgia of the thumb following a bone felon; one was associated with prominent livedo reticularis; one was associated with purpura; two followed mild frost-bite. The result was excellent in all the patients save one. The exceptional patient (Case 2) was definitely improved, with cessation of attacks of vasospasm from emotional excitement but persistence of annoying sensitivity to cold. There has been no further alteration in his symptoms during the two years of observation. Six of the patients had varying degrees of scleroderma, in most instances very pronounced. In all of these there has been a considerable improvement in the scleroderma; the skin is softer and the digits are more mobile. Whenever digital ulcers or gangrenous patches were present they healed promptly and have not recurred. The patient in whom there was arthritis of the hands in addition to Raynaud's disease has not only been relieved of the attacks of vasospasm but has had considerable improvement in the arthritis. The girl with livedo reticularis has shown much improvement in this regard.

In Table IV are listed sympathectomies on twenty extremities in which preoperative studies demonstrated that the circulatory deficiency was due entirely or almost entirely to occlusive disease with little or no element of vasospasm. These patients are the sort for whom sympathectomy has ordinarily been felt to offer no benefit. No definite promise of help was offered to any of them, and the operation was carried out with the understanding that it was done more or less as an experimental procedure. The results are very interesting. Case 46 has already been discussed. There were several other poor results. Case 48 is that of a young man who had had a severe frostbite and who had pronounced obliterative disease with gangrene of one toe, cellulitis of the foot, and severe pain. After sympathectomy the toe was amputated. There remains a tiny ulcer at the site of amputation and the foot is still cold, but the patient has pain on walking only occasionally and feels that he was helped a great deal.

Case 50 in this group is that of a young man with rapidly progressive Buerger's disease and severe resting pain who was not helped by sympathectomy. There was some relief from alcohol injection of the posterior tibial nerve, but the patient refused other peripheral nerve interruption or other treatment, persisted in smoking heavily, and left the hospital determined to have an amputation of the leg. One patient (Case 53) with arteriosclerosis, intermittent claudication, an infected ulcer of the leg, and severe resting pain had complete relief of pain for several weeks following sympathectomy. The pain returned, however, after his discharge, the ulcer failed to heal, and amputation was carried out. The other leg has been entirely comfortable since operation. One patient (Case 47) was an unfortunate young man with Buerger's disease, intermittent claudication, and severe resting pain who had undergone amputation of four toes with failure of healing of two, hundreds of hours of paxev therapy, intermittent venous occlusion, the intravenous administration of hypertonic salt solution, alcohol injection of peripheral nerves, and other measures during the past six years, during which time his disability progressed steadily. There was no demonstrable element of vasospasm, and right lumbar sympathectomy was performed at his request as an experimental procedure. There was almost complete relief of pain but no progress in healing of the ulcers. Because of the relief of pain the other extremity was sympathetomized, with good result. Amputation of the right leg was necessary.

In the other cases the result was surprisingly good. The complete relief of symptoms in Case 42 has been discussed. Cases 45 and 54, which appeared hopeless, had relief of very severe pain, healing of ulcers, and improvement in warmth and color. In Case 44, a diabetic with poor circulation and a perforating ulcer of the sole of the foot which had showed no improvement during six months of good treatment, healing took place promptly after operation. In another patient (Case 51) with diabetes and severe arteriosclerosis there was healing of a

TABLE I  
RESULTS OF SYMPATHECTOMY IN VASOSPASTIC DISEASE

CASE NUM- BER	UNIT NUMBER	SEX	AGE	DIAGNOSIS	DURATION OF SYMP- TOMS	SYMPATHECTOMY, DATE	RESULTS	PERIOD OF FOLLOW- UP
1	186027	F	44	Raynaud's disease with rapidly progressive scleroderma	2 yr.	Right dorsal, 1/15/40 Left dorsal, 1/25/40	Attacks of vasospasm ceased; scleroderma improved	2 yr.
2	115967	M	35	Raynaud's disease	4 yr.	Left dorsal, 3/11/40 Right dorsal, 4/8/40	Attacks of vasospasm from emotional excitement ceased; little improvement in coldness of hands on exposure to cold	2 yr.
3	198080	F	29	Raynaud's disease with scleroderma and digital ulcers	11 yr.	Left dorsal, 4/27/40 Right dorsal, 5/7/40	Attacks of vasospasm ceased; no further ulcers, scleroderma improved, fingers more mobile	2 yr.
4	114184	M	38	Raynaud's disease with scleroderma; loss of right finger 4 from gangrene. Contracture of right finger 5	5 yr.	Left dorsal, 4/9/40 Right dorsal, 8/25/41	Scleroderma greatly improved in left hand, moderately in right; attacks of vasospasm ceased	2 yr.
5	189243	M	33	Hyperhydrosis, elephantiasis, diffuse subcutaneous hemangioma	33 yr.	Right lumbar, 5/1/40	Sweating ceased; elephantiasis treated with good result by Homans' operation	2 yr.
6	202048	F	18	Severe vasospasm and livedo reticularis	2 yr.	Right lumbar, 7/25/40 Left lumbar, 8/1/40	No further coldness or numbness; livedo much improved.	21 mo.

TABLE IV

SYMPATHECTOMY IN CASES OF ORBITERATE ALTERNAL DISEASE WITH LITTLE OR NO VASOSPASM

CASE NO.	UNIT NO.	SEX	AGE	DIAGNOSIS AND SYMPTOMS	DURATION OF SYMPTOMS	PROGNOSIS FROM SKIN TEMP. STUDIES	SYMPATHECTOMY, DATE	RESULT	PERIOD OF FOLLOW-UP
42	241492	M	46	Right axillary arterial thrombosis, mild diabetes, weakness, pain and numbness in hand and forearm, coldness, cyanosis, objective sensory loss	6 wk.	Poor to fair	Right dorsal, 10/6/41	Almost completely well. Warm hand, muscle power good, no pain, no objective sensory loss	6 mo.
43	224970	M	40	Buerger's disease; healed ulcer of right great toe, Coldness of right foot, pain in right foot on walking 3 blocks	8 mo.	Poor to fair	Left lumbar, 3/12/41 Right lumbar, 3/22/41	Feet warmer and of good color; very little discomfort, walks farther, still smoking	1 yr.
44	196805	F	62	Arteriosclerosis, diabetes, perforating ulcer on foot from puncture wound; no healing	6 mo.	Poor	Right lumbar, 12/22/41	Ulcer healed promptly and has remained healed	4 mo.
45	232670	M	35	Buerger's disease; lost left great toe from gangrene. Unhealed toes, stumps of right 2, 4, and 5. Extreme resting pain	4 yr.	Very poor	Right lumbar, 1/23/42 Left lumbar, 1/29/42	Pain completely relieved. Ulcers healed rapidly, feet warmer and of better color	3 mo.
46	226911	M	47	Buerger's disease; ulcers of left foot for 1 yr. Migrating phlebitis, resting pain, claudication (3-4 blocks)	12 yr.	(?) Unsatisfactory because of infection	Left lumbar, 1/29/41	Returned to work before ulcers healed; still unhealed, slight if any improvement	15 mo.
47	197211	M	34	Buerger's disease, severe resting pain, claudication, loss of right toes, 2, 3, 4, 5; unhealed stump	6 yr.	Nil	Right lumbar, 5/2/40 Left lumbar, 5/10/40	Pain relieved but no progress in healing of ulcer of right foot; right Callander amputation done 5/20/40. Left leg comfortable, foot slightly warmer and of better color	1 mo.



48	219569	M	20	Post-frostbite obliterative arterial disease, resting pain; gangrene of right great toe, cellulitis foot.	10 mo.	Nil	Right lumbar, 1/21/41	Toe amputated 2/18/41, tiny ulcer at site persists; occasionally some pain on walking, foot still cold. Patient feels he was helped considerably	15 mo.
49	222813	M	55	Post-frostbite obliterative arterial disease, loss of a number of toes from gangrene, ulcer of left foot, cellulitis and lymphangitis	22 yr.	Nil	Right lumbar, 3/21/41 Left lumbar, 3/31/41	Ulcer healed; feet slightly warmer and of better color	1 yr.
50	223436	M	25	Buerger's disease; very severe resting pain	9 mo.	Nil	Left lumbar, 3/13/41	Pain continued. Alcohol injection left posterior tibial nerve gave little relief. Patient persisted in smoking, refused further peripheral nerve section, and other treatment; left hospital to have amputation elsewhere	3 wk.
51	243415	M	63	Arteriosclerosis, diabetes, gangrene of distal end of first toe, with osteomyelitis; osteomyelitis of fifth toe	9 mo.	Nil	Left lumbar, 10/29/41 Amputation fifth toe, 12/3/41	Amputation stump healed per pyrim. Gangrenous ulcer of first toe healed	6 mo.
52	130061	M	58	Arteriosclerosis, claudication of right thigh ( $\frac{1}{2}$ block); burning pain in foot and impending gangrene in toes	2 yr.	Nil left Good right	Bilateral lumbar, 11/19/41	Feet warmer and of better color; resting pain relieved but claudication unimproved	5 mo.
53	245441	M	57	Arteriosclerosis, claudication (1 block), resting pain, ulcer of right leg (4 months)	6 yr.	Nil	Right lumbar, 11/26/41 Left lumbar, 12/29/41	Pain relieved at first but returned after several weeks as ulcer increased in size; right Calander operation done 12/29/41. Patient now comfortable.	4 mo.
54	255653	M	43	Buerger's disease; unhealed amputation stump of right fourth toe. Impending gangrene of right toes 2 and 3. Severe resting pain	4 mo.	Nil	Right lumbar, 3/23/42 Left lumbar, 3/28/42	Marked pain relief, ulcer healed; increased warmth and better color	1 mo.

SYMPATHECTOMY IN CASES OF OBSTRUCTIVE ARTERIAL DISEASE WITH A CONSIDERABLE ELEMENT OF VASOSPASM

CASE NO.	UNIT NO.	SEX	AGE	DIAGNOSIS AND SYMPTOMS	DURATION OF SYMPTOMS	PROGNOSIS FROM SKIN TEMP. STUDIES	SYMPATHECTOMY, DATE	RESULT	PERIOD OF FOLLOW-UP
27	185417	M	29	Buerger's disease, coldness and numbness, resting pain, foot pain on exercise (1 block); unhealed stump from amputation left toe 4	2 yr.	Good	Left lumbar, 11/16/39 Right lumbar, 11/24/39	Ulcer healed, feet dry, warm, comfortable, walks well; working	6 mo.
28	209372	M	51	Buerger's disease and coldness, intermittent claudication (50 yds.); right femoral occlusion	4 yr.	Good	Right lumbar, 9/5/40 Left lumbar, 9/11/40	Feet warm; walking distance increased to 3 1/2 blocks. No further improvement. Developed diabetes Dec, 1941	20 mo.
29	149430	M	31	Buerger's disease; left supracondylar amputation 2 yr. previously. Ulcers of right leg for 6 months	3 yr.	Fair	Right lumbar, 11/16/40	Ulcers healed rapidly; in spite of persistent smoking and neglect of foot, it remained well for 16 mo. then foot cooled and 2 small ulcers developed. Healing with rest	17 mo.
30	297575	M	33	Buerger's disease; gangrene of left foot, intermittent claudication (1 block)	6 mo.	Good, right, nil left	Right lumbar, left Cal. under amputation, 4/18/41	Greatly improved; some aching leg and foot on first using artificial limb. Working	1 yr.
31	121897	M	38	Syphilis, tabes, and (1) Buerger's disease; feet cold and wet. Two perforating ulcers of right foot	5 1/2 yr.	Excellent	Right lumbar, 4/25/41	Foot hot and dry; ulcer healed promptly and in spite of exceedingly poor foot cure has remained healed	1 yr.
32	293153	M	55	Post-frostbite obliterative disease; feet cold, numb and painful. Has had pain in heels for years	5 mo.	Good	Left lumbar, 5/12/41 Right lumbar, 5/19/41	Symptoms disappeared except for discomfort in heels which is somewhat better	11 mo.

33	221757	M	43	Buerger's disease. Intermit- tent claudication (1 block)	6 mo.	Fair	Left lumbar, 5/5/41	Foot warm; walking dis- tance increased to 3 blocks	11 mo.
34	226040	M	35	(?) Buerger's disease and pain and fatigue in calves unrelieved by elastic sup- port; coldness and wetness of feet. Very small va- rices	4 yr.	Excel- lent	Left lumbar, 7/17/41 Right lumbar, 7/28/41	Feet warm and dry; discom- fort persists but is con- siderably better	9 mo.
35	243185	M	59	Arteriosclerosis, left femoral arterial thrombosis, dia- betes, intermittent claudi- cation, resting pain and numbness; objective anes- thesia foot and ankle	5 mo.	Good	Left lumbar, 10/30/41	Foot warmer and of better color, other symptoms un- improved; anesthesia un- improved	6 mo.
36	141314	M	50	Buerger's disease and syph- ilis; right foot cold and wet, claudication (1½ blocks). Recurrent throm- bophlebitis of left leg.	10 yr.	Good	Right lumbar, 11/22/41 Left lumbar, 12/2/41	Feet warm, no claudication, no resting pain, no further attacks of phlebitis, no edema left leg	5 mo.
37	252612	M	43	Buerger's disease and mi- grating phlebitis; cold, wet feet. Resting pain.	5 yr.	Good	Left lumbar, 2/18/42 Right lumbar, 2/24/42	All symptoms relieved	2 mo.
38	252670	M	29	Buerger's disease, has lost parts of several digits from gangrene. Infected gangrene of the left first and third fingers	5 yr.	Fair	Left dorsal, 2/21/42 Right dorsal, 2/28/42	Hands warmer and comfort- able; gangrenous digits well demarcated and free of infection	2 mo.
39	224159	M	67	Arteriosclerosis, gangrenous ulcer of right great toe with osteomyelitis; severe resting pain	5 wk.	Good	Right lumbar, 3/19/42	Pain relieved, distal end phalanx removed; healing	1 mo.
40	255252	M	52	Buerger's disease; pain and numbness walking or ex- posure to cold	4 yr.	Fair	Right lumbar, 3/24/42 Left lumbar, 3/28/42	Symptom-free; feet warm	1 mo.
41	177405	M	39	Werner's syndrome, obliter- ative arterial disease, scler- oderma, calcinosis, and ar- teriosclerosis; ulcer over tendo achillis	?	Good	Right lumbar, 12/3/41	Foot warmer, otherwise no change; ulcer being treated by tubed graft	4 mo.

TABLE III

SYMPATHECTOMY IN CASES OF OBSTRUCTIVE ARTERIAL DISEASE WITH A CONSIDERABLE ELEMENT OF VASOSPASM

CASE NO.	UNIT NO.	SEX	AGE	DIAGNOSIS AND SYMPTOMS	DURATION OF SYMP-TOMS	PROGNO-SIS FROM SKIN TEMP. STUDIES	SYMPATHECTOMY, DATE	RESULT	PERIOD OF FOLLOW-UP
27	185417	M	29	Buerger's disease, coldness and numbness, resting pain, foot pain on exercise (1 block); unhealed stump from amputation left toe <sup>4</sup>	2 yr.	Good	Left lumbar, 11/16/39 Right lumbar, 11/24/39	Ulcer healed, feet dry, warm, comfortable, nicks well; working	6 mo.
28	209372	M	31	Buerger's disease and coldness, intermittent claudication (50 yds.); right femoral occlusion	1 yr.	Good	Right lumbar, 9/5/40 Left lumbar, 9/11/40	Feet warm; walking distance increased to 3½ blocks. No further improvement. Developed diabetes Dec., 1941	20 mo.
29	149130	M	31	Buerger's disease; left sciatic amputation 2 yr. previously. Ulcers of right leg for 6 months	3 yr.	Fair	Right lumbar, 11/16/40	Ulcers healed rapidly; in spite of persistent smoking and neglect of foot, it remained well for 16 mo. then foot cooled and 2 small ulcers developed. Healing with rest	17 mo.
30	227575	M	33	Buerger's disease; gangrene of left foot, intermittent claudication (1 block)	6 mo.	Good	Right lumbar, left Calander amputation, 4/18/41	Greatly improved, some aching leg and foot on first using artificial limb	1 yr.
31	121897	M	38	Syphilis, tabes, and (9) Buerger's disease; feet cold and wet. Two perforating ulcers of right foot	5½ yr.	Excellent	Right lumbar, 4/25/41	Foot hot and dry; ulcer healed promptly and in spite of exceedingly poor foot care has remained healed	1 yr.
32	223153	M	55	Past frostbite obliterative disease; feet cold, numb and painful. Has had pain in heels for years	5 mo.	Good	Left lumbar, 5/12/41 Right lumbar, 5/19/41	Symptoms disappeared except for discomfort in heels which is somewhat better	11 mo.

One case of Werner's syndrome is included. Because of the frequency of development of severe nutritional difficulties in the limbs of patients with this disease, one limb was sympathectomized in order to see whether with the passage of time this limb would fare better than the other. The answer to this question must wait for some years. Definite improvement was noted in all the others. The extremities have become warmer and of better color. Resting pain has been relieved in all instances save one. In this patient (Case 35) there was intense pain and numbness in a cold anesthetic foot which followed femoral arterial thrombosis. Sympathectomy was done five months after the vascular accident; although the circulation in the foot is significantly better than it was before operation, the anesthesia, pain, and numbness persist. Whether regeneration will take place and relief of symptoms ensue one cannot say. Interestingly enough, another patient listed in Table IV had similar anesthesia and painful paresthesias in a limb after axillary arterial thrombosis, underwent a sympathectomy six weeks after the occlusion, and within a month noted beginning return of sensation and has subsequently had complete relief of symptoms. Two patients complained of pain in the feet on exercise and both were relieved by sympathectomy. Five had intermittent claudication in the calves. One is unimproved, three are moderately improved, and one is apparently entirely relieved of this symptom. Five patients had ulcers or gangrenous digits. Healing occurred in three, and in two recently operated upon satisfactory healing seems to be taking place. Several who had had attacks of phlebitis have had no attacks since operation. No amputations have been necessary.

Case 29 is of particular interest. This 31-year-old patient with severe Burger's disease had had an amputation of the left leg two years previously and for six months had had two ulcers of the lower portion of the right leg. Sympathectomy was followed by improvement in circulation and rapid healing of the ulcers. The patient continued to smoke to excess, to subject himself and especially his foot, to long exposure to cold, and in general to neglect his foot. For one year the circulation was excellent; then the foot began to get cooler and slightly cyanotic, and two small ulcers appeared. They are healing with bed rest. Another patient (Case 46, Table IV) is similarly interesting. He is a 47-year-old man with severe Burger's disease who had mi-grating phlebitis, intermittent claudication, several ulcers of the left foot of a year's duration, and resting pain. He had undergone a lumbar sympathectomy fifteen months previously. The foot improved in color and warmth and the ulcers appeared to be healing when he left the hospital. He returned to work immediately and the ulcers failed to heal. One cannot say with certainty that these two patients would have done better had they had better care after operation, but I believe they illustrate the necessity for the best possible care after sympathectomy has been performed.

had chronic leg ulcers. In two instances in which the ulcers were very large and were associated with much induration, sympathectomy was combined with wide and deep excision of the ulcer and skin grafting. All of the ulcers healed promptly. In two there were slight recurrences which healed with pressure dressings. All of the patients who had had phlebitis had some degree of discomfort in the affected extremity, and in all of them the discomfort was relieved or diminished after operation. Cutaneous hyperesthesia was prominent in several, disappearing in all of them following operation. In some instances the edema was unchanged following operation, in some it has been less. Two patients were operated upon who had recurrent attacks of thrombophlebitis, in one of whom the attacks were of very long duration. One of these patients has continued to have attacks with almost as great frequency as before operation but they are now much milder and of shorter duration. The other patient has shown more improvement in this respect, having had only a single brief and mild attack during the twenty months since sympathectomy. This patient had an enormous elephantoid limb and was told before operation that reduction in size would almost certainly require a plastic operation of the type Homans has described. One accident occurred in this group. The patient in Case 17 had small pulmonary emboli after operation which were treated by ligation of the iliac veins. One patient had a very painful ulcer which developed in an uncomfortable edematous limb in which he had sustained a fracture of the fibula many years previously. There was no definite history of thrombophlebitis. His ulcer, which had been so indolent and painful that he had been tempted to accept his physician's advice and undergo amputation, healed promptly after sympathectomy and discomfort ceased.

Two patients with sickle-cell anemia and chronic leg ulcers were operated upon in an effort to learn whether sympathectomy might be of some aid in the solution of this very difficult problem. In neither could there be demonstrated any evidence of vasospasm before operation. One patient seems to have been helped somewhat; in the other the operation was apparently of no benefit.

*Sympathectomy in Obliterative Arterial Disease.*—Forty lumbar and three dorsal sympathectomies were performed upon twenty-eight patients with various sorts of obliterative arterial disease. Seventeen had definite or probable thromboangiitis obliterans; six had arteriosclerosis, four of them being diabetics; three had obliterative arterial disease following severe frostbite; one diabetic in whom there was no evidence of peripheral arteriosclerosis had an axillary arterial thrombosis; one patient had Werner's syndrome. In Table III are grouped twenty-three sympathectomies on extremities in which there was a considerable element of vasospasm. Included are all those patients in whom occurred a rise of digital skin temperature to 28.5° C. or more after inhibition of vasoconstrictor impulses.

20	246266	M	30	Postphlebitic ulcer, edema and pain	6 yr.	Right lumbar, 11/22/41	Ulcer healed, pain diminished	5 mo.
21	246105	M	37	Postphlebitic ulcer and pain	4 yr.	Left lumbar, 11/25/41	Ulcer healed promptly, small pin point recurrence when started to work; controlled with pressure bandage. Pain gone.	5 mo.
22	245430	M	29	Postphlebitic edema, cutaneous and subcutaneous hypereesthesia	1 yr.	Left lumbar, 11/26/41	Pain and hyperesthesia gone, edema less	5 mo.
23	247544	M	27	Postphlebitic ulcer and edema	8 yr.	Left lumbar; excision ulcer, skin grafts, 12/3/41	Ulcer healed, edema less, discomfort less; working	5 mo.
24	221680	M	43	Post-traumatic (fracture) edema with painful ulcer	35 yr. ulcer 10 mo	Skin graft, 2/17/41 Right lumbar, 2/24/41	Ulcer had previously been excised and grafted without healing and amputation had been advised; ulcer healed rapidly after sympathectomy. Back at work with no pain	14 mo.
25	147393	M	27	Sickle-cell anemia; leg ulcer; syphilis	4 yr.	Right lumbar, 10/2/40	Ulcer had been twice excised and grafted but never stayed healed more than 3 months; healed after sympathectomy and stayed healed until traumatized 10 months later. Healed with grafts	1 yr.
26	224804	M	20	Sickle-cell anemia; leg ulcer; syphilis	9 yr.	Left lumbar, 3/6/41; skin grafts, right lumbar, 3/15/41	Ulcers recurred in 3 months	4 mo.

TABLE II

RESULTS OF SYMPATHETOMY FOR PHLEBITIC SQUELAE AND CHRONIC LEG ULCERS

CASE NUM- BER	UNIT NUMBER	SEX	AGE	DIAGNOSIS	DURATION OF SYM- TOMS	SYMPATHETOMY, DATE	RESULT	PERIOD OF FOLLOW- UP
14	201612	F	52	Recurrent femoral thrombo- phlebitis, postphlebitic ede- ma, pain and vasospasm	13 yr.	Left lumbar, 6/21/40	Discomfort less, edema slightly improved, no vasospasm; at- tacks of phlebitis continue but milder and of shorter duration	22 mo.
15	131399	M	56	Postphlebitic ulcer and ede- ma	32 yr.	Left lumbar, 9/3/40; ex- cision ulcer and skin graft 9/19/40	Ulcer healed rapidly with no further difficulty; doing hard labor	20 mo.
16	218107	F	37	Postphlebitic elephantoid state; chronic and recur- rent femoro-iliac phlebitis	14 yr.	Right lumbar, 9/9/40	Only one brief recurrence of thrombophlebitis; leg much more comfortable but swelling persists	20 mo.
17	106934	M	38	Postphlebitic ulcer and ede- ma	5 yr. ulcer 3 yr.	Left lumbar, 9/23/40	Had small pulmonary embol, treated by iliac vein ligation Ulcer healed. Small ulcer re- curred 5 mo. later; healed with pressure bandage. Work- ing	19 mo.
18	227848	M	32	Postphlebitic pain and edema	10 yr.	Left lumbar, 5/2/41	Discomfort gone, edema less; legs active life	1 yr.
19	238665	M	49	Postphlebitic ulcer	3 yr.	Left lumbar, 8/25/41	Ulcer healed, edema less	8 mo.



7	186944	F	52	Raynaud-like syndrome; caus- algia right thumb	3½ yr.	Right dorsal, 10/28/40	Pain entirely gone; hand re- mains warm	18 mo.
8	221998	M	35	Raynaud's disease with ede- ma and rash on hands and feet, scleroderma ears	10 yr.	Left lumbar, 3/4/41 Right lumbar, 3/13/41 Right dorsal, 4/16/41 Left dorsal, 4/25/41	No further attacks of vaso- spasm, edema, or rash; scler- oderma improved	1 yr.
9	215934	F	24	Vasospasm of the legs with purpura and edema; old history of frostbite	7 yr.	Right lumbar, 4/9/41 Left lumbar, 4/14/41	No further coldness or numb- ness and edema less; purpura continues but is controlled with elastic stocking	1 yr.
10	225486	F	60	Raynaud's disease with slight scleroderma; edema of hands, gangrenous ulcer on left index finger	5 mo.	Left dorsal, 4/12/41 Right dorsal, 4/21/41	Edema and attacks of vaso- spasm ceased, ulcer healed promptly; patient died 2 months later of Rickettsia-like fever	2 mo.
11	203914	F	19	Raynaud's disease with scler- oderma	5 yr.	Right dorsal, 8/9/41 Left dorsal, 8/16/41	No further attacks of vaso- spasm; scleroderma improved	8 mo.
12	175179	F	42	Raynaud's disease; arthritis in hands	10 yr.	Right dorsal, 11/26/41 Left dorsal, 12/2/41	No further attacks of vaso- spasm; edema disappeared, mobility improved and arthri- tis considerably improved	5 mo.
13	108840	F	38	Post-frostbite vasospasm	3 yr.	Right lumbar, 3/20/42 Left lumbar, 3/24/42	Attacks of vasospasm and of burning pain ceased	1 mo.

gangrenous toe in which there was x-ray evidence of osteomyelitis and primary healing of the amputation stump following removal of another toe in which there was extensive chronic osteomyelitis. Case 49 is that of a man who, during a period of 22 years, had gradually lost parts of most of his toes from gangrene following a severe frost-bite. A chronic ulcer of the foot healed promptly after operation. One patient (Case 52) with arteriosclerosis, intermittent claudication in the thigh, burning pain in the foot, and impending gangrene of several toes has had noticeable improvement in circulation and relief from resting pain. The claudication continues. Case 43 is a man with Buerger's disease who complained of coldness of his foot and pain on walking a few blocks. He showed definite improvement in circulation following operation and could walk without discomfort.

It should be stated that almost all of the patients with obliterative arterial disease had had the usual nonoperative treatment before operation—exercises, pavex, intermittent venous occlusion, intravenous administration of saline solution, intravenous sodium thiosulfate injections, and abstinence from smoking. Some had undergone prolonged and intensive treatment. It is also of interest that various forms of nonoperative treatment have been tried since operation in a few of the patients who had residual symptoms without any further improvement.

#### DISCUSSION

Sympathectomy should receive full consideration as a means for the treatment of peripheral vascular disease. Every patient with obliterative arterial disease of the extremities and those with annoying vasospastic disease merit careful study to see whether they may be helped by sympathectomy. Before any patient is subjected to sympathectomy he should be studied carefully in an effort to evaluate the possible benefit from this procedure from the standpoint of release of vasospasm, relief of pain, and reduction in heat loss through sweating and evaporation. Sympathectomy will probably find a wider field of applicability in the treatment of other disorders of the peripheral circulation.

No matter how striking the improvement after sympathectomy, patients should continue to take the best of care of their extremities and to do everything possible to prevent progress of the disease and to further the development of collateral circulation. Those with arterial circulatory deficiency should not smoke, should avoid exposure to extremes of temperature, should take exercise to the point of tolerance, and should take special exercises to promote collateral circulation. Every patient who has undergone sympathectomy should keep the extremity well greased in order to avoid excessive dryness of the skin.

Sympathectomy gives excellent results in the treatment of Raynaud's disease and the other purely vasospastic arterial circulatory deficiencies. Ordinarily, the extremities become warm and dry and ase. In a small percentage of cases, as in one

of mine, there are no further attacks from emotional stimuli but the extremities continue to cool abnormally on exposure to cold. The proper explanation for this small group of less favorable cases is difficult to find. The current tendency is to ascribe the result to too much "local fault." In the vasospastic disorders, as in most diseases, the earlier the stage at which treatment is undertaken the better the result obtained. Results are certainly better in those cases in which there are no pathologic alterations in skin or bone. In the present series all instances of scleroderma were improved, in some patients very strikingly. There was no further spread, the skin became softer, contracted stiff fingers became more movable. There are cases, however, in which less favorable results are obtained. It seems fair to say that improvement will take place in scleroderma in most instances, that in some there will be little improvement but the progress of the disease will be stopped, and that in others the progress of the disease will be definitely slowed. Digital ulcers may be expected to heal and not to recur.

In the common obliterative arterial diseases, thromboangiitis and arteriosclerosis, much can be accomplished by sympathectomy. The circulation often improves noticeably, sweating ceases and with it the tendency to maceration and to epidermophytosis, ulcers often heal, and impending gangrene frequently disappears. There is commonly the most gratifying relief of resting pain. If the relief should not be complete, judicious application of peripheral nerve interruption, as suggested by White, will prove of great benefit. Pain on exercise presents a more difficult problem. The pain which some patients experience in their feet on walking is ordinarily relieved. The typical intermittent claudication of the calves, however, is the symptom for which sympathectomy accomplishes least. Sometimes there is no improvement at all in the distance the patient can walk, although actual pain may be replaced by a sense of fatigue. Occasionally there is striking relief of intermittent claudication. More often there is moderate increase in the distance walked before onset of pain. To increase the walking distance from half a block to three or four blocks is not a spectacular improvement, but it may mean the difference between a very restricted life and a fairly active one.

In general, the good effects which may be expected from sympathectomy can be fairly well assayed by careful study before operation. Whenever there is disagreement between the evaluation arrived at from preoperative studies and the actual result of operation, the result obtained is always better than the one anticipated. Experiences such as those recorded in Table IV illustrate the fact that certain patients in whom no significant element of vasospasm can be demonstrated may profit remarkably by sympathectomy. Consequently, I feel that in cases of apparently pure or almost pure obliterative arterial deficiency certain ones which appear hopeful to those experienced in this field may justifiably be subjected to sympathectomy. It must be remembered that this is a relatively safe operation with a short and comfortable con-

valescence. If a number of major amputations can be saved in this manner one need not regret a few futile efforts. It should be stated emphatically, however, that the routine use of sympathectomy without any attempt at selection of cases and without proper preoperative study would be most inadvisable and would only bring discredit to the procedure. It is my impression that in any patient with obliterative arterial disease and significant vasospasm, one can accomplish fully as much, probably more, with a short period of hospitalization and a simple operative procedure as one can hope to accomplish by almost daily treatments with the pavex boot, intermittent venous occlusion, various sorts of intravenous injections, and other so-called conservative measures. The timesaving and moneysaving element of this choice of treatment is a most important consideration to most of the patients, many of whom come for help only after they have become impoverished by prolonged medical treatment and inability to work.

Patients with sequelae from frostbite are an interesting group. Some of them have no demonstrable evidence of obliterative disease but present a more or less typical Raynaud syndrome. Such patients respond beautifully to sympathectomy. Others have varying degrees of obliterative arterial disease. The role of sympathectomy in their treatment is much the same as in the other obliterative arterial diseases. Proper treatment at the time of the initial frostbite will undoubtedly reduce greatly the number of patients who have vascular symptoms thereafter. It is my feeling that lumbar sympathetic procaine block is probably the most effectual treatment for such cases. If one or more such injections should fail to give lasting benefit one should not hesitate to proceed directly with operative sympathectomy.

Similarly, the proper care of those suffering from acute thrombophlebitis will undoubtedly reduce the number who develop phlebitic sequelae. Sympathetic block, suggested by Leriche and introduced in this country by Ochsner and his associates, is a valuable aid in the treatment of acute thrombophlebitis. Proper and sufficient bed rest until there is little or no edema when the affected limb is dependent, and the use of elastic support as long as there is the slightest edema are other important measures. Such care will decrease the number of patients who will subsequently suffer from swollen painful limbs, intractable ulcers, hyperesthesia, and recurrent episodes of thrombophlebitis. Sympathectomy seems to have a definite place in the treatment of certain of these sequelae, although its status is in certain respects still in the experimental stage. From my experience with two cases it is not felt that sympathectomy will prevent further attacks in cases of recurrent thrombophlebitis, but it can be expected to decrease the duration and severity of attacks. Perhaps it may prove useful in this regard in combination with ligation of the vein. Sympathectomy affords considerable or complete relief from the annoying discomfort that so commonly exists after phlebitis, especially in those patients with cutaneous hyperesthesia and vasospasm. It has a definite place in the man-

of mine, there are no further attacks from emotional stimuli but the extremities continue to cool abnormally on exposure to cold. The proper explanation for this small group of less favorable cases is difficult to find. The current tendency is to ascribe the result to too much "local fault." In the vasospastic disorders, as in most diseases, the earlier the stage at which treatment is undertaken the better the result obtained. Results are certainly better in those cases in which there are no pathologic alterations in skin or bone. In the present series all instances of scleroderma were improved, in some patients very strikingly. There was no further spread, the skin became softer, contracted stiff fingers became more movable. There are cases, however, in which less favorable results are obtained. It seems fair to say that improvement will take place in scleroderma in most instances, that in some there will be little improvement but the progress of the disease will be stopped, and that in others the progress of the disease will be definitely slowed. Digital ulcers may be expected to heal and not to recur.

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# MEASUREMENT OF THE CIRCULATION RATE

## A REVIEW OF THE METHODS

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### INTRODUCTION

THE methods proposed for determining the rate of blood flow in the vessels are numerous, and one confronted with the task of measuring this velocity must evaluate carefully all the factors involved in the particular type of cases to be studied. Circulation rate, which is the time required for blood to be transported from one point in a vessel to a definite distant point, is expressed most accurately in terms of distance per unit time, as centimeters per second. Clinically, however, the circulation rate has come to mean just the time required for the transport, in order to differentiate it from the circulation time, which has been defined by Koch:<sup>47</sup> "By circulation time is understood the time required for a blood particle to traverse an entire circulation." Obviously, since the circulation time may be long or short depending on the choice of the vessels selected by the indicator, circulation time is rarely determined clinically.

Blumgart<sup>5</sup> has written a good discussion of blood velocity, and with his collaborators<sup>69</sup> has stated that, in order to be used in testing the circulation rate, the indicator should: (a) be nontoxic in the amounts used, (b) not itself influence the velocity of flow at the time of determination, (c) with its effect, disappear rapidly, (d) have a short reaction time, and (e) be applicable to normal and pathologic cases.

The following review is intended as a survey of the history of circulation rate determination.

### METHODS

Volkman, in 1850, used the pressure of the blood as a measure of its velocity, replacing a segment of the blood vessel with a hairpin-shaped glass tube filled with water, an instrument to which he applied the name haemodromometer. Vierordt, in 1858, inserted a pendulum-like device in the vessel lumen, the velocity being calculated from the extent of deflection, an instrument he called the haemotachometer, and which was later modified by Chauveau, Bertolus, and Laroyen.<sup>12</sup> Cybulski's photohemotachometer<sup>14</sup> was a variation of the same principle. Similarly, the differential manometers of Frank<sup>22</sup> and Daly,<sup>15</sup> though differing from each other in principle, have the common disadvantage of requiring insertion into a divided vessel. The stromuhr, even in the experimental

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agement of postphlebitic ulcers, especially when they are small and the surrounding tissue is not too indurated. In cases of large ulcers with much induration, wide deep excision of the affected tissue and skin grafting should be carried out. If such patients have demonstrable vasospasm this procedure may be combined profitably with sympathetic denervation.

Sympathectomy gives excellent results in certain cases of causalgia. In cases of post-traumatic edema and osteoporosis and other vasospastic states, as well as in "phantom-limb pain," it should be carried out if relief has been obtained with procaine block of the sympathetic nerves provided a permanent cure cannot be effected by one or several procaine injections.

#### SUMMARY

The value of sympathectomy in the treatment of disorders of the peripheral circulation has been discussed. The study of patients in an attempt to evaluate the possible benefit of sympathectomy is outlined, the operative technique of dorsal and lumbar sympathectomy is described, and the results in sympathetic denervation of eighty-three extremities are presented.

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# MEASUREMENT OF THE CIRCULATION RATE

## A REVIEW OF THE METHODS

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### INTRODUCTION

THE methods proposed for determining the rate of blood flow in the vessels are numerous, and one confronted with the task of measuring this velocity must evaluate carefully all the factors involved in the particular type of cases to be studied. Circulation rate, which is the time required for blood to be transported from one point in a vessel to a definite distant point, is expressed most accurately in terms of distance per unit time, as centimeters per second. Clinically, however, the circulation rate has come to mean just the time required for the transport, in order to differentiate it from the circulation time, which has been defined by Koch:<sup>47</sup> "By circulation time is understood the time required for a blood particle to traverse an entire circulation." Obviously, since the circulation time may be long or short depending on the choice of the vessels selected by the indicator, circulation time is rarely determined clinically.

Blumgart<sup>5</sup> has written a good discussion of blood velocity, and with his collaborators<sup>69</sup> has stated that, in order to be used in testing the circulation rate, the indicator should: (a) be nontoxic in the amounts used, (b) not itself influence the velocity of flow at the time of determination, (c) with its effect, disappear rapidly, (d) have a short reaction time, and (e) be applicable to normal and pathologic cases.

The following review is intended as a survey of the history of circulation rate determination.

### METHODS

Volkman, in 1850, used the pressure of the blood as a measure of its velocity, replacing a segment of the blood vessel with a hairpin-shaped glass tube filled with water, an instrument to which he applied the name haemodromometer. Vierordt, in 1858, inserted a pendulum-like device in the vessel lumen, the velocity being calculated from the extent of deflection, an instrument he called the haemotachometer, and which was later modified by Chauveau, Bertolus, and Laroyen.<sup>12</sup> Cybulski's photohemotachometer<sup>14</sup> was a variation of the same principle. Similarly, the differential manometers of Frank<sup>22</sup> and Daly,<sup>15</sup> though differing from each other in principle, have the common disadvantage of requiring insertion into a divided vessel. The stromuhr, even in the experimental

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animal, was proved by Dogiel<sup>16</sup> to be inaccurate, the velocity varying from turn to turn. By prolonging the time of observation, however, Burton-Opitz<sup>11</sup> was able to use the recording stromuhr successfully. The thermostromuhr of Rein<sup>57</sup> stands as a magnificent tribute to the genius of its inventor, blood volume flow between two points in a vessel being calculated from the thermal change after a definite quantity of heat has been applied to the vessel wall.

These devices, however suitable for the experimental animal, cannot be employed clinically, and investigators have suggested numerous methods by means of which circulation rate may be determined with less trauma, and, perhaps, with more directness. Vierordt<sup>67</sup> previously had made use of the "*muscae volitantes*" of Aristotle, measuring the capillary blood velocity in his own eye by projection of the image of a moving corpuscle on a white surface and obtaining a rate of 0.5 mm. per second as capillary blood velocity. Even before this, Hering<sup>33</sup> had determined the jugular-to-jugular time in a horse by injecting potassium ferrocyanid into one jugular vein and determining the time of arrival in the opposite jugular by the Prussian blue reaction, finding that the jugular-to-jugular and jugular-to-tarsal times were nearly the same. Vierordt, however, obtained the blood samples for testing in little cups fixed to a disk rotating at a definite rate, an instrument he described as the hemotachometer, a method which was highly refined in the hands of Hermann<sup>34, 35</sup> and Ainser and Lohe.<sup>1</sup> Very accurate determinations of circulation rate between different arbitrary points in the experimental animal have been made by these investigators.

Using this principle, many substances have been utilized. Koch<sup>46</sup> injected fluorescein into one vessel and collected blood samples on a Vierordt disk. Meyer<sup>53</sup> used methemoglobin obtained from a donor animal, determining its arrival time spectroscopically, and Thompson, Alper, and Thompson<sup>65</sup> injected brilliant vital red solution in man, securing blood samples from the same vein every fifteen seconds. Similarly, Klein and Heinemann<sup>45</sup> used Congo red solution, Heilmeyer and Riemsehneider<sup>31</sup> determining the instant of arrival spectroscopically. Stewart<sup>64</sup> injected methylene blue into the rabbit vein and determined its arrival time in the retina by direct inspection. Bornstein<sup>10</sup> administered a single deep inspiration of air containing 5 to 7 per cent carbon dioxide, and determined the interval between the inspiration and the first deep inspiration to follow involuntarily, assuming this interval to be circulation time between the lung capillaries and the respiratory center. Franck and Alvens<sup>21</sup> roentgenographically determined the arrival of bismuth oil at a second point in a vessel after injection at a first point. Frimann-Dahl<sup>23</sup> measured the interval between the injection of Per-Abrodil, a radiopaque iodine-containing substance, into the saphenous vein and its roentgenographic appearance in the femoral vein. Hirschsohn and Maendel<sup>43</sup> and Kahler<sup>41</sup> used the intravenous injection of 5 c.c. of a 10 per cent solution of calcium chloride, which was followed

by a feeling of warmth and burning in the throat, and which they believed was due to the arrival of the salt at the nerve endings in the tissues, the warm feeling gradually extending to the chest, abdomen, pubis, arms, legs, and feet, in an inconstant order. Leschke<sup>48</sup> used calcium bromide for this purpose with a similar effect.

Blumgart and his co-workers<sup>6, 9</sup> studied circulation rate by injecting radium C at one point and determining its arrival at another point by a counting chamber, an exceedingly accurate clinical method but one equally tedious and elaborate. Edmunds<sup>17</sup> and Stewart,<sup>61-63</sup> however, had injected concentrated sodium chloride solution intravenously into animals and determined its arrival at one point by the change in conductivity of the vessel placed between two nonpolarizable electrodes. Meldolesi applied this method to human beings in 1925, using an electrode placed near the observation point in a galvanometer circuit.

Neubauer,<sup>54</sup> experimenting on the choleric action of bile salts, found that a side action of dehydrocholic acid was its bitter taste, and Winternitz, Deutsch, and Brüll<sup>71</sup> using this substance as "decholin" first described its action as a determiner of circulation time to the tongue, a method which Gargill<sup>24</sup> has tested and found to be practicable. Eppinger<sup>18</sup> first recognized the applicability to this problem of the skin flushing after intravenous histamine injection, the method having been used clinically in over 600 determinations by Wollheim and Lange.<sup>72</sup> The principal objection to this method, observed by Harmer and Harris,<sup>29</sup> aside from its limited observable circuit, is the fall in blood pressure and great increase in pulse rate which accompanies the reaction. Fishberg, Hitzig, and King<sup>20</sup> found that saccharine introduced into a vein caused a sweet taste, the interval between injection and the signal by the patient being the time for passage through the vein, to and through the heart and lungs to the tongue. The reaction time of the patient is included. Webb, Sheinfeld, and Colin<sup>68</sup> measured the interval between the intravenous injection of a small quantity of ether and its detection in the breath of the subject by the observer.

Geppert, in 1889,<sup>26</sup> observed an increase in respiratory depth in animals after intravenous injection of calcium cyanide during his studies on the mechanism of hydrocyanic acid asphyxiation. Gasser and Loevenhart<sup>25</sup> then used sodium cyanide as a respiratory stimulant in animals in an attempt to show that stimulation of the respiratory center was due to diminished oxidation, observing that the respiratory response in the rabbit after external jugular injection was "surprisingly rapid" (within three seconds). A few years later, Loevenhart and his colleagues<sup>52</sup> applied the method clinically, Robb and Weiss<sup>58</sup> finding later that the toxic dose of sodium cyanide was twenty times that required for a respiratory response. These workers used a 2 per cent solution in water and concluded that the cyanide was excreted as hydrogen cyanide by the lungs, as cyanides and sulfocyanides by the urine, and that the remainder was converted into relatively innocuous sulfur compounds.

The question as to the exact site of action of sodium cyanide in producing the hyperpnea has been debated. The fact that HCN is one of the strongest respiratory stimulants known (Heinz<sup>32</sup>) has led some to believe that this action of cyanide is directly on the respiratory center (Robertson;<sup>59</sup> Loevenhart and associates;<sup>28, 49, 51</sup> Gesell and co-workers;<sup>27, 56, 70</sup> and Heffter<sup>30</sup>). However, in 1927, Hertzman and Gesell<sup>36</sup> in cross circulation experiments had evidence that cyanide could exert its stimulating action with the head isolated. This work was followed

TABLE I

CIRCULATION TIMES AS DETERMINED BY VARIOUS OBSERVERS WITH DIFFERENT METHODS (TIMES IN SECONDS)

TIME	ROUTE	METHOD	OBSERVER
20-25	jugular-to-jugular (horse)	ferrocyanide	Hering <sup>33</sup>
14-59	jugular-to-jugular	ferrocyanide	Ainser and Lohe <sup>1</sup>
18-23	cubital-to-cubital (man)	fluorescein	Koch <sup>46, 47</sup>
16-18	femoral-to-right atrium (dog)	bismuth oil	Franck and Alwens <sup>21</sup>
9-15	cubital-to-mouth (man)	calcium chloride	Kahler <sup>44</sup>
10-12	cubital-to-skin (man)	calcium chloride and bromide	Leschke <sup>48</sup>
6	cubital-to-opposite radial artery (man)	Congo red	Klein and Heine- mann <sup>45</sup>
4-7.6	lesser circulation (dog)	conductivity	Romm <sup>60</sup>
3.5-7.1	greater circulation (dog)	conductivity	Romm <sup>60</sup>
8.9-12.8	entire circulation (dog)	conductivity	Romm <sup>60</sup>
13-30	cubital-to-face	histamine	Weiss, Robb, and Blumgart <sup>69</sup>
14-24	cubital-to-opposite brachial (man)	radium C	Weiss, Robb, and Blumgart <sup>69</sup>
15-20	cubital-to-tongue (man)	decholin	Gargill <sup>24</sup>
8-14	cubital-to-tongue (man)	decholin	Winternitz et al. <sup>71</sup>
12.5-18	cubital-to-carotid (man)	sodium cyanide	Gargill <sup>24</sup>
8-16	femoral vein-to- carotid (dog)	sodium cyanide	Winder, Winder and Gesell <sup>70</sup>
1	through heart (man)	radium C	Blumgart and Weiss <sup>7</sup>
6.5	lesser circulation (man)	radium C	Blumgart and Weiss <sup>8</sup>
10.7	cubital-to-tongue (man)	saccharine	Webb, Sheinfeld, and Colin <sup>68</sup>
6.3	cubital-to-lung (man)	ether	Webb, Sheinfeld, and Colin <sup>68</sup>

by the painstaking, ingenious studies of Heymans and his collaborators,<sup>37-42</sup> who have proved that the carotid sinus is the origin of the respiratory reflexes, that in the dog cyanide acts on the sinus with little or no effect on the center, that there is an instantaneous effect on respiration after injection of cyanide into the common carotid artery, that the action of cyanide on the center is depressive, and that no response to

cyanide is obtained if both carotid sinuses are denervated. These researches have been confirmed by Bernthal<sup>4</sup> and Comroe and Schmidt.<sup>13</sup>

The only objections to the use of sodium cyanide in the determination of circulation rate relate to the effect on the heart, which may alter the true rate by the salt itself. Barnard,<sup>2</sup> Loevenhart and Eyster,<sup>50</sup> Evans,<sup>19</sup> and Bellis<sup>3</sup> have shown that cyanide increases the force, rate, and amplitude of the heart, but these effects occur simultaneously with the respiratory response and cannot, therefore, be taken to influence it. Another objection to the methods of determining circulation rate by intravenous indicators such as sodium cyanide arises from the observations of Tigerstedt<sup>66</sup> that the speed of the central or axial portions of a stream may be twice that of the peripheral portions, but this, although true for constant flow in rigid tubes of constant diameter, does not hold for the blood stream with its turbulence due to pulse, elastic walls, contained cells, and varying diameters of the vessels.

By way of comparison, Table I is presented to show the values obtained for circulation rates by the corresponding observers using various methods. The purely objective response obtained after the injection of sodium cyanide intravenously greatly simplifies its routine use. With this advantage is coupled that of application in colored individuals (where histamine cannot be used).

#### SUMMARY

A brief historical review of the methods which have been used for the determination of the circulation rate has been presented. This information formed the basis for selecting sodium cyanide as the determinant in surgical patients. These results are described in a succeeding paper.

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# THE CIRCULATION RATE AFTER OPERATION

WITH SPECIAL REFERENCE TO THE EFFECT OF POSITION

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## INTRODUCTION

IT MUST be evident, to even a casual observer, that opening the abdomen upsets a finely adjusted circulation-respiration equilibrium, the delicate interplay of whose components is responsible for normal circulatory efficiency. As a group, therefore, surgeons are, perhaps, more interested in acute changes in circulatory dynamics, and with good reason, for circulatory collapse, during surgery or immediately after, points an accusing finger at the surgeon. It is well known that the human body has an almost incredible, but limited, power to adjust itself to unusual demands on its circulation. In fact, Harvey<sup>10</sup> wrote, "The circuit of blood is accomplished now more rapidly, now more slowly according to the temperament, age, and so forth of the individual, to external and internal circumstances, to naturals and non-naturals—sleep, rest, food, exercise, affections of the mind, and the like—."

Frimann-Dahl,<sup>9</sup> who has advocated the theory of slowed venous flow as the most important factor in postoperative thrombosis, showed roentgenographically that the movements of the diaphragm, which acts as a pump on the veins inferior to it, are shallower after operation; especially is this decreased pumping action evident on the veins of the upper abdomen. Men were more affected in this manner than were women, but the effect in women was more protracted. He found that the saphenous-to-femoral venous flow in patients undergoing operations predisposing to thrombosis was reduced to a standstill. Flow in the arm veins, however, was not so retarded. Postoperative distention caused considerable venous stasis. He, therefore, attributed the slowing of saphenous flow to (a) abdominal distention leading to increased intra-abdominal pressure and to (b) inactivity of patients. Bellis and Wangenstein<sup>1</sup> have confirmed the retarding effect of intestinal distention on venous return from the lower extremities in man and in the experimental animal.

Lanzara<sup>16</sup> determined the decholin time in sixty-six cases pre-operatively and postoperatively. He usually found a shortened post-operative time, the figures remaining within normal limits, however.

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Webb, Sheinfeld, and Colin<sup>30</sup> stated that no significant differences between preoperative and postoperative circulation rates were present when determined by the saccharin and ether method. They also stated that laparotomy, spinal anesthesia, morphine, slight elevation of pulse and temperature, and moderate abdominal distention did not affect the circulation rate. Inspection of their table of eight cases subjected to spinal anesthesia, however, shows that every patient experienced a shortened circulation time after the procedure. In one individual, the time after the anesthetic was nine seconds shorter than before.

Since the effect of operation on circulation rate is apparently open to discussion, the question was reopened in the investigations to be described.

#### METHOD

Using the sodium cyanide method, the cubital-to-carotid and ankle-to-carotid circulation times were determined in 191 cases preoperatively

TABLE IA

CUBITAL VEIN TO CAROTID BODY AND ANKLE VEIN TO CAROTID BODY CIRCULATION TIMES (SECONDS) DETERMINED PREOPERATIVELY AND POSTOPERATIVELY BY THE SODIUM CYANIDE METHOD

TYPE OF OPERATION	NO. OF CASES	CUBITAL-TO-CAROTID*		ANKLE-TO-CAROTID*	
		PRE-OPERATIVE	POST-OPERATIVE	PRE-OPERATIVE	POST-OPERATIVE
Appendectomy	21	13 (8-20)	10 (8-15)	30 (20-41)	28 (18-47)
Cholecystectomy	18	15 (8-26)	12 (8-24)	35 (20-63)	28 (18-45)
Neck dissection and thyroidectomy	17	15 (9-28)	14 (9-29)	39 (25-67)	35 (27-41)
Craniotomy	15	20 (11-35)	15 (13-20)	36 (28-42)	34 (22-45)
Herniorrhaphy	14	15 (8-25)	13 (7-23)	31 (17-58)	38 (18-65)
Colostomy	8	25 (8-92)	15 (10-25)	38 (28-54)	34 (23-60)
Kidney-ureter	7	17 (11-32)	16 (12-21)	30 (15-45)	28 (24-31)
Exploratory laparotomy	7	17 (11-30)	15 (10-14)	38 (30-46)	31 (27-35)
Hemorrhoidectomy	7	13 (8-19)	12 (8-17)	30 (25-45)	33 (23-47)
Gastric resection	6	23 (13-30)	16 (10-17)	48 (30-85)	30 (23-42)
Posterior rectectomy	6	15 (10-17)	14 (8-19)	37 (26-52)	30 (20-37)
Radical mastectomy	6	12 (8-16)	12 (8-17)	31 (20-49)	30 (21-36)
Miscellaneous†	59	16 (7-31)	14 (8-31)	41 (15-95)	38 (21-80)
Total	191	17 (7-92)	14 (7-31)	36 (15-95)	32 (18-80)

\*Range enclosed in parenthesis below average for each group.

†Lumbar sympathectomy, transurethral resection, breast biopsy, suprapubic cystostomy, rectal polypectomy, drainage ischiorectal abscess, cardiomyolysis, perineal proctectomy, gastroenterostomy, presacral neurectomy, drainage pancreatic abscess, lip excision, splenectomy, amputation of penis, enterostomy, leg amputation, closure perforated ulcer, excision mandible, axillary dissection, scrotal-crural fixation, ligation external carotid, etc.

TABLE IB

CASE	PREOPERATIVE				POSTOPERATIVE			
	CUBITAL- TO- CAROTID	ANKLE- TO- CAROTID	PULSE	TEM- PERA- TURE	CUBITAL- TO- CAROTID	ANKLE- TO- CAROTID	PULSE	TEM- PERA- TURE
<i>1. Appendectomy</i>								
1	13	--	82	99.0	12	--	82	96.6
2	11	--	100	98.0	8	--	106	100.0
3	13	29	68	98.6	10	29	104	104.4
4	12	22	100	99.2	15	23	96	99.4
5	9	28	104	98.6	9	30	86	100.0
6	12	--	72	97.2	11	--	80	99.2
7	12	20	92	--	9	20	128	98.8
8	20	36	60	--	11	40	--	--
9	--	30	100	99.0	--	47	80	98.8
10	11	25	80	98.0	11	18	80	100.0
11	20	41	96	98.0	12	30	82	99.4
12	12	37	--	--	12	35	80	--
13	10	22	68	97.8	9	19	100	99.8
14	8	20	88	99.3	7	22	100	100.6
15	15	38	76	--	11	33	83	--
16	16	26	80	98.6	8	20	102	99.0
17	10	41	72	98.4	10	34	84	99.8
18	13	33	74	99.0	10	30	76	100.2
19	12	28	68	98.6	13	20	80	100.0
20	9	38	82	--	10	--	94	--
21	12	27	80	--	8	--	80	--
Avg.	13	30			10	28		
<i>2. Cholecystectomy, Choledochotomy, and Cholecyst-gastrostomy</i>								
1	10	35	84	99.2	10	18	92	100.2
2	18	--	88	98.6	14	--	132	101.8
3	26	63	72	98.8	24	45	64	100.0
4	12	25	80	98.0	10	30	96	98.6
5	10	28	84	98.6	12	28	88	99.0
6	13	25	84	98.2	16	23	92	98.8
7	12	20	80	97.8	8	24	112	99.8
8	18	40	68	98.6	12	20	100	101.0
9	15	--	60	98.6	10	--	--	--
10	10	33	112	98.4	10	22	96	100.4
11	23	32	100	98.4	12	24	104	100.0
12	23	--	70	97.4	24	--	--	--
13	14	36	78	99.4	10	33	76	100.0
14	14	40	74	98.8	12	25	78	99.8
15	17	35	74	97.8	9	31	88	99.4
16	11	43	76	98.0	10	38	78	100.2
17	8	--	82	97.8	9	--	100	--
18	15	--	--	--	11	--	--	--
Avg.	15	35			12	28		
<i>3. Thyroidectomy and Neck Dissection</i>								
1	28	67	72	97.8	23	40	60	98.4
2	11	--	104	99.0	11	--	--	--
3	28	--	78	98.4	29	--	--	--
4	17	26	84	98.0	15	27	--	--
5	9	25	84	99.6	14	31	92	99.0
6	10	27	104	97.4	12	27	84	98.2
7	15	--	--	--	15	--	--	--
8	12	--	--	--	16	--	--	--
9	14	36	--	--	14	42	--	--
10	17	--	--	--	16	--	--	--
11	12	--	80	98.8	10	--	100	99.8
12	10	38	76	99.0	10	39	88	100.2
13	14	45	78	99.4	9	40	104	100.6
14	13	40	90	--	12	--	110	--
15	13	--	74	--	11	28	106	--
16	14	45	76	98.6	12	41	85	99.8
17	10	40	70	97.8	10	33	78	100.0

TABLE IB--CONT'D

CASE	PREOPERATIVE				POSTOPERATIVE			
	CUBITAL- TO- CAROTID	ANKLE- TO- CAROTID	PULSE	TEM- PERA- TURE	CUBITAL- TO- CAROTID	ANKLE- TO- CAROTID	PULSE	TEM- PERA- TURE
<i>4. Craniotomy (including ventriculograms, explorations, and trigeminal rhizotomies)</i>								
1	35	--	86	99.0	20	--	104	--
2	21	42	86	98.6	15	45	72	--
3	21	28	88	97.4	15	32	84	99.8
4	24	--	80	97.4	13	--	80	98.8
5	15	28	92	98.0	14	23	94	100.8
6	28	35	72	98.6	20	31	--	--
7	20	--	--	--	15	--	80	99.6
8	11	29	80	98.6	14	22	100	101.2
9	29	42	68	97.8	14	42	80	100.6
10	14	--	64	98.0	15	--	76	98.6
11	22	--	64	98.0	17	--	92	101.0
12	16	--	136	99.2	13	--	100	100.8
13	14	39	82	--	14	39	76	--
14	16	38	78	99.0	18	40	80	100.4
15	11	--	--	--	10	--	--	--
Avg.	20	36	--	--	15	34	--	--
<i>5. Herniorrhaphy (inguinal and ventral)</i>								
1	18	42	78	98.6	14	40	76	--
2	15	--	88	99.0	12	--	118	100.0
3	12	18	100	--	12	16	--	--
4	9	--	72	98.0	7	--	82	99.6
5	17	28	68	98.6	10	53	88	100.6
6	25	55	74	98.4	23	54	60	98.6
7	8	17	132	98.8	10	18	131	100.4
8	14	33	76	98.0	13	39	80	99.2
9	14	35	68	98.6	10	35	88	98.6
10	22	31	52	97.0	19	65	76	100.0
11	13	--	76	98.6	15	--	--	--
12	18	--	76	99.2	16	--	--	--
13	13	22	84	98.0	11	23	86	100.4
14	13	--	--	--	10	--	--	--
Avg.	15	31	--	--	13	38	--	--
<i>6. Colostomy</i>								
1	92	39	68	98.6	25	33	80	99.4
2	17	40	80	98.4	17	37	74	99.0
3	18	27	92	--	15	25	--	--
4	17	47	84	97.4	15	37	--	--
5	15	32	72	100.2	13	23	--	--
6	24	54	76	96.4	12	60	76	99.4
7	11	28	--	--	10	24	--	--
8	8	--	--	--	10	--	--	--
Avg.	25	38	--	--	15	34	--	--
<i>7. Kidney and Ureter (including pelviolithotomy, ureterolithotomy, nephrostomy, and ureteropelvioplasty)</i>								
1	32	45	80	98.4	20	30	80	100.2
2	18	37	80	98.6	21	27	120	98.6
3	15	30	84	99.0	15	24	120	102.0
4	11	16	100	98.0	17	24	--	--
5	16	15	100	98.2	12	31	112	98.2
6	12	35	80	--	12	28	86	--
7	12	34	80	99.4	12	35	84	100.8
Avg.	17	30	--	--	16	28	--	--
<i>8. Exploratory Laparotomy</i>								
1	15	30	96	97.2	13	28	--	--
2	13	36	72	97.4	13	34	--	--
3	17	40	72	--	12	27	108	98.8
4	15	35	96	98.2	8	23	124	99.8
5	30	40	76	98.6	19	30	72	99.0
6	15	46	--	--	10	44	--	--
7	12	37	--	--	10	35	--	--
Avg.	17	38	--	--	15	31	--	--

TABLE IB—CONT'D

CASE	PREOPERATIVE				POSTOPERATIVE			
	CUBITAL- TO- CAROTID	ANKLE- TO- CAROTID	PULSE	TEM- PERA- TURE	CUBITAL- TO- CAROTID	ANKLE- TO- CAROTID	PULSE	TEM- PERA- TURE
<i>9. Hemorrhoidectomy</i>								
1	13	45	78	98.2	8	47	80	99.4
2	9	27	82	98.6	11	27	88	100.2
3	9	30	--	--	--	44	--	--
4	8	25	--	--	16	23	--	--
5	14	28	80	100.0	17	26	82	99.8
6	16	30	76	99.0	9	35	86	101.0
7	19	26	74	98.8	11	31	100	100.2
Avg.	13	30			12	33		

and postoperatively. The first determination in each individual was made about twenty hours before operation, the second determination about twenty hours after operation. Of the cases listed (Table I, A), 132 could be classified in groups according to operative procedure; 59 were miscellaneous procedures. The type of anesthetic employed varied, and many of the operations were not laparotomies. "Nervous" patients, those with varices of the lower extremities, and children were not investigated. Every determination was made with the trunk horizontal and the extremities in the plane of the trunk, the veins into which the injections were made being approximately at heart level, and the patient instructed against muscular movement. It was frequently necessary to elevate the injected extremity by a pillow in order to bring the vein used to the level of the anterior axillary fold.

Because the organism seems to respond better to a second stimulus by sodium cyanide than to a first, the response to injection was first determined from one of the cubital veins, and following a five-minute interval (the time required for the destruction and elimination of the salt), an injection into one of the ankle veins was made. The cubital-to-carotid time or ankle-to-carotid time is the time recorded by an observer with a stop watch between the intravenous injection and the first deep inspiration to follow. This includes the time required for the stimulant to travel from the intravenous needle point to and through the heart and pulmonary circulation to the carotid body. Although Loevenhart, Lorenz, Martin, and Malone<sup>18</sup> used injections of 3 to 5 mg. of sodium cyanide, we used  $\frac{2}{10}$  to  $\frac{5}{10}$  of a c.c. of a 2 per cent solution (4 to 10 mg.) for the arm vein and  $\frac{5}{10}$  to 1 c.c. (10 to 20 mg.) for the ankle vein, the amount varying principally with the patient's apparent weight. In no case was the patient informed of the response expected, this rule being adhered to in order to avoid any subjective influence. Occasionally, the response is associated with symptoms suggestive of motor irritation, lasting less than a minute; in some cases a slight temporary nausea was noted, but in none was there any alarming sequela. Care was taken to allow none of the solution to be injected extravascularly, since such an accident may be followed by a local necrosis.

## EFFECT OF POSITION ON CIRCULATION RATE

In order to study the effect of position of an extremity on the circulation rate of sodium cyanide injected into one of its veins, twenty-six cases were selected. In ten of these (Table II, A), the antecubital-to-carotid time was determined in the dorsal decubitus with the arm: (1) in the plane of the trunk, (2) elevated perpendicular to the trunk, and (3) dependent perpendicular to the trunk. When injections were made into elevated extremities, the needle was inserted into the vein with the extremity horizontal, the extremity then being elevated for one or two minutes with the needle and syringe in place, following which the injection was made.

In four individuals, similar determinations were made on the lower extremities (Table II, B).

TABLE II

## EFFECT OF POSITION ON CIRCULATION TIME (SODIUM CYANIDE METHOD)\*

<i>A. Cubital Vein-to-Carotid Body Times With Upper Extremity Positioned (Patient Horizontal)</i>			
CASE	ARM HORIZONTAL	ARM ELEVATED	ARM DEPENDENT
1	12	12	15
2	18	14	20
3	17	17	27
4	17	18	22
5	15	17	15
6	12	11	16
7	11	13	16
8	10	10	14
9	14	15	20
Avg.	14	14	18
<i>B. Ankle Vein-to-Carotid Body Times With Lower Extremity Positioned (Patient Horizontal)</i>			
CASE	EXTREMITY HORIZONTAL	EXTREMITY ELEVATED	EXTREMITY DEPENDENT
1	60	21	70
2	45	17	30
3	29	23	60
4	48	20	--
<i>C. Ankle Vein-to-Carotid Body Times in Trendelenburg (Head Down, 30°) and Reverse Trendelenburg (Feet Down, 30°) Positions</i>			
CASE	HORIZONTAL	TRENDELENBURG	REVERSE TRENDELENBURG
1	26	25	31
2	35	20	42
3	35	25	66
4	43	18	150
5	over 2 minutes	22	no response
6	28	27	no response
<i>D. Ankle Vein-to-Carotid and Cubital Vein-to-Carotid Body Times in Fowler's Position</i>			
	CUBITAL-TO-CAROTID	ANKLE-TO-CAROTID (DORSAL DECUBITUS)	ANKLE-TO-CAROTID (FOWLER'S)
	15	25	no response
	13	28	no response
	15	19	no response
	17	20	no response
	13	31	no response
	12	20	no response

\*Times in seconds.

In six cases a comparison was made between ankle vein-to-carotid times in the horizontal, Trendelenburg,  $30^{\circ}$  (head down, legs up), and reverse Trendelenburg,  $30^{\circ}$  (head up, legs down), positions.

In another group of six cases the ankle vein-to-carotid body time was determined with the patient in dorsal decubitus and in Fowler's position.

In two individuals, the effect of active movement of the foot and toes on the ankle vein-to-carotid body time in the dorsal decubitus position was determined.

### RESULTS

From an inspection of Table I, it can be seen that, generally, one may expect to find a slightly shorter circulation time following such operations as are listed during the immediate postoperative period, especially following laparotomies. In the 191 cases listed, the average preoperative cubital-to-carotid and ankle-to-carotid times were seventeen and thirty-six seconds, respectively. In every individual, the cubital-to-carotid time was shorter than the ankle-to-carotid time. It should be noted that the circulation time varies between widely separated extremes in different patients. To obtain an idea of the individual case variations in circulation rate and the relation of these rates to the pulse and temperature at the time of determination, these data are included in Table I, *B*, which constitutes the largest case groups.

In the dorsal decubitus position, the antecubital-to-carotid time with the arm in the plane of the trunk averaged fourteen seconds; with the arm elevated perpendicular to the trunk, fourteen seconds; and with the arm dependent perpendicular to the trunk eighteen seconds (Table II, *A*).

In the dorsal decubitus position, the ankle-to-carotid time with the lower extremity at body level was sixty seconds, with the extremity dependent seventy seconds, and with the extremity elevated twenty-one seconds. In another individual, the horizontal time was forty-five seconds, but in the dependent position was reduced to thirty seconds; however, when elevated, the time was seventeen seconds. The values in the third and fourth cases are what might be predicted (Table II, *B*).

With the extremities in the plane of the trunk, the ankle vein-to-carotid time in six individuals was found to be, typically, thirty-five seconds with the trunk horizontal, twenty seconds in the Trendelenburg position, and forty-two seconds in the reverse Trendelenburg position (Table II, *C*).

In only one of six patients placed in Fowler's position could a response-to-ankle vein injection be elicited; in fact, in two cases, perivascular necrosis occurred at the point of injection, the venous pressure being so high in that position as to force the solution out the vein through the needle puncture. In each case, however, a response was noted when the patient was brought from Fowler's to the horizontal position (Table II, *D*).

In the dorsal decubitus position, active movement of the foot and toes in one individual decreased the ankle vein-to-carotid body time from thirty-two seconds in the resting state to thirty seconds in the active; in another individual the time was decreased from forty-five seconds in the resting state to twenty-one seconds in the active state.

#### DISCUSSION

The slight decrease in circulation time following operation may be due to the effect of the increased temperature and respiration on the pulse rate, a possibility entirely in accord with the observation that in none of the tabulated cases was there a great deal of postoperative abdominal distention.

The direct explanation of the slightly greater velocity of blood flow postoperatively is to be found in the cardiovascular system. Koeh<sup>14</sup> has stated that the blood velocity is affected by the time of day, season, climate, heart force, stroke output, viscosity of the blood, pulse frequency, absorption of food, menses, pregnancy, age, and respiration. The most obvious explanation for the faster blood flow postoperatively is the elevation of body temperature with its corresponding increase in heart rate, Berns<sup>2</sup> having shown experimentally that artificial fever accelerates the blood flow in dogs. A fast blood circulation in fever was also observed by Wollheim and Lange<sup>31</sup> and Lian and Faquet.<sup>17</sup>

For a similar reason, blood flow is accelerated in thyrotoxicosis, and conversely, retarded in myxedema (Blumgart, Gargill, and Gilligan<sup>3, 4</sup>). Hering had insisted that cardiac rate did not influence circulation rate, and Steinhilber,<sup>26</sup> observing a slower pulse in the dog after vagotomy, concluded that circulation time was prolonged by increased heart rate. Tarr, Oppenheimer, and Sager<sup>27</sup> and Tigerstedt<sup>28</sup> have affirmed that circulation time has little or no relationship to heart rate or arterial blood pressure, but Vierordt showed that there was a positive correlation between pulse rate and circulation rate, a finding substantiated by Blumgart and Weiss<sup>5</sup> using radium C, who found, however, that a considerable increase in heart rate only increased the blood flow slightly.

Apparently, dependency of the upper extremity retards the return of its blood to the heart, although, conversely, a faster return in the elevated position could not be demonstrated. This is probably due to the fact that the emptied veins lack a sufficient medium in which the stimulant can be transported. The possibility that the Fowler's position tends toward venous stasis in the lower extremities should be seriously considered, especially in those conditions where thrombophlebitis is often an unhappy accompaniment. Frimann-Dahl<sup>9</sup> showed in four patients that raising the extremity increased the rate of venous flow. He, therefore, urged postoperative elevation of the lower extremities or the foot of the bed and frequent active movement of the legs.

Piorry<sup>21</sup> in his classical paper on posture and blood flow first called attention to the impediment to circulation in the standing still posi-

tion, proposing that syncope was due to encephalic anemia resulting from stasis below the heart. He further stated that arterial, venous, and capillary circulation were all dependent on position, and that it was gravity that caused veins to distend when the arm was dependent. Incidentally, it was he who called attention to the effect of gravity on the production of hypostatic pneumonia.

Since the brilliant researches of Piorry, confirming observations have appeared in large numbers. Among these are the investigations of Bock, Dill, and Edwards<sup>6</sup> and Thompson, Alper, and Thompson<sup>28</sup> who showed that the circulation rate is much longer (1.5 to 4.5 times) in the standing than in the recumbent position. Lawrence, Hurxthal, and Bock<sup>15</sup> observed a downward gradient of blood flow on going from the recumbent to the sitting to the standing positions. Specifically, in an athlete who had won eight of eighteen Marathon races, there was a reduction of 25 per cent in blood flow on going from the recumbent to the sitting position, and a reduction of 40 per cent in the standing position, the flow in the recumbent position being taken as the standard. By a different method, Rosen and White<sup>23</sup> came to the same general conclusions.

The effect of position on venous pressure is well known, von Recklinghausen<sup>22</sup> having observed a venous pressure in the foot equivalent to the hydrostatic difference between the foot and the heart. He concluded that the force of the heartbeat alone was insufficient to raise the venous blood from the feet to the heart in the vertical position. His original observations have been confirmed many times, Schott<sup>24</sup> having shown that the venous pressure in the foot is increased as the difference in the hydrostatic level between the foot and right atrium is increased. Hill and Barnard<sup>11</sup> have calculated that in a man six feet high the hydrostatic pressure of a column of blood from the vertex to the sole is about 140 mm. Hg, and from the vertex to the middle of the abdomen about 50 mm. Hg. It is, therefore, understandable why the Fowler's position retards the venous return from the lower extremities and pelvis.

Mogk<sup>20</sup> measuring directly the brachial venous pressure in dogs, found a 400 per cent increase after exercise. Burton-Opitz<sup>8</sup> found that in dogs venous flow from a limb was increased during muscular contraction and that the pressure also rose. Braune<sup>7</sup> described the mechanism by which the venous stream to the right heart from the lower extremities is accelerated by muscular movement, and later Kaufmann<sup>13</sup> demonstrated in the horse that muscular activity (mastication) causes blood to spurt from an open vein (of the masseter muscle). In the human being, Meinertz<sup>19</sup> found that the venous pressure in the hand turning a centrifuge was 1 to 8 cm. of water higher than in the inactive hand. Sewell<sup>25</sup> found that the venous pressure in the hand rose 3.4 to 5.3 mm. Hg on alternately clenching the fist, observations which have been confirmed by those of Hooker.<sup>12</sup>



## SUMMARY

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**Asepsis.**—It seems unnecessary in our present stage of enlightenment to more than mention the need of strict asepsis, yet infractions of the rules still occur. Failure to mask both mouth and nose of everyone in the room and handling of the transfixions without a recently boiled hemostat may result in septic grief. Skin incisions for insertion of transfixions, use of medicated dressings, or redressing of pin wounds will only propagate further sequelae.

Late pin-wound infections are often produced by senile, youthful, or uncooperative patients who insist upon scratching the wound with

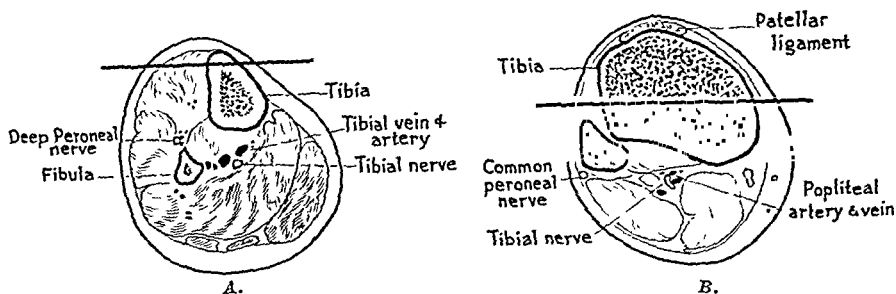


Fig. 1.—A. Improper placement of transfixions is the most prolific source of sequelae. For instance, piercing the crest of the tibia is physiologically and mechanically unsound. The bone is so dense that the friction of drilling generates enough heat to cause a local thermal coagulation with subsequent ring necrosis. Focusing all the skeletal traction force on a small avascular area frequently results in a pressure "sore." Drilling in such hard bone causes the pin to wobble with a resulting loose fit of pin in bone. Coupled with narrowness of the bone at this level, this makes for instability.

B. In this case the lazy way is the correct way. Insertion of the pin through the wide, cancellous bone, near but not into the joint, is easily done and supplies excellent control. Traction pressure is distributed equally to many little partitions. Multiplicity of honeycombed cells minimizes subsequent scularity assures immunity and early repair.

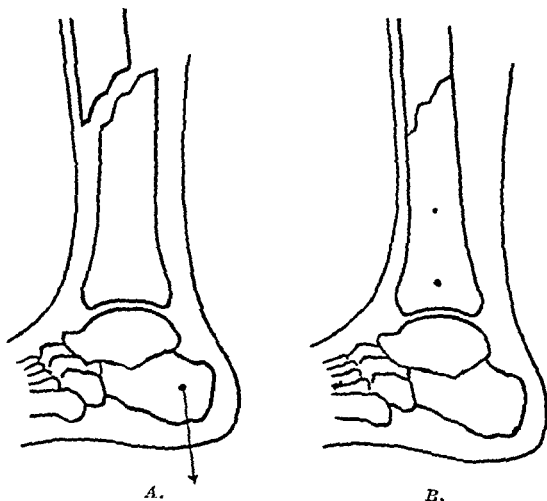


Fig. 2.—A. Skeletal transfixation of the os calcis supplies traction, but control of the distal tibial fragment is lost through mobility of the two intervening joints. B. Transfixion of the fragment itself serves a triple purpose: (1) direct traction, (2) positive control, and (3) absolute fixation. Whenever it is necessary to transfix the cortical or shaft portion of the femur, a slender pin or wire is preferable, provided it is kept taut.

## SEQUELAE OF TRANSFIXATION OF BONE

ROGER ANDERSON, M.D., SEATTLE, WASH., AND

B. L. FINLAYSON, M.D., PRICE, UTAH

A CRITICAL search for the cause of undesirable sequelae of bone transfixation in fracture therapy leads one to conclude that they arise not from the use but from the misuse of transfixions. Further analysis reveals the misuse is usually due to fear, unpreparedness, or haste, with resultant failure to observe the following dictums of bone transfixation.

1. Proper placement of the transfixions
2. Fixation of the transfixions to their respective fragments
3. Control of forces available through transfixation

The most prolific source of complication is the improper placement of transfixions. Fear of violating a joint has erroneously led the "authorities" to advocate transfixing the shaft of bones. Such piercing of the shaft, still insisted upon by even the most recent textbooks, is fraught with danger. Not only are the shafts narrow but the cortical bone is so dense that it contains the minimum blood supply. When all the traction and countertraction pressure exerted by a pin is focused upon such a relatively small area of poorly vascularized bone, a pressure necrosis may result, much in the same manner that a sustained pressure on the big toe of a patient with Buerger's disease will precipitate a local gangrene. Why penetrate the shaft when the wide, richly vascular, honeycombed diaphysis can be more safely and quickly transfixed.

Placement of the transfixion in a bone beyond the distal fragment, such as the os calcis for tibial shaft fractures or through the crest of the tibia for femoral shaft fractures, is not infrequently productive of complications. Such placement in an adjacent bone, while it may supply sufficient traction, cannot prevent loss of reduction or movement between fragments, with the possibility of delayed union. However, when the transfixions are placed directly through the fragments, they supply not only traction and countertraction but positive fixation.

*Insertion.*—Surprising as it may seem, the actual process of fast drilling of a large pin through dense bone such as the shaft of the tibia will generate so much heat at the pin point that an actual local cauterization occurs. Such coagulation and burning of the haversian canals cause an *aseptic thermal necrosis*. Results of this lethal heating will be expressed, one or more months later, in the form of a doughnut-like or ring sequestrum.

While thermal necrosis usually results from improper placement or use of dull pin points, it may result from inserting pins or half-pins at excessive speeds with a hand drill or electric motor.

in movement between fragment and transfixion, with their share of sequelae, are noted below.

1. Failure to angularly insert two transfixions into each fragment, or to fix firmly the single transfixion or parallel transfixions into the fragment by some positive means, such as a snug-fitting cast.



Fig 4—A, Sterility of transfixions should be assiduously preserved. The ordinary lifting forceps and bottle should be ostracized because it is invariably polluted after it is used a few times.

B, Covering of the nose as well as the mouth of everyone in the room is imperative. Placing of corks over both ends of the transfixion keeps the pin points sharp and prevents their falling through holes in the tiav. Pins should not be touched with the gloved hand but only with a recently boiled hemostat.

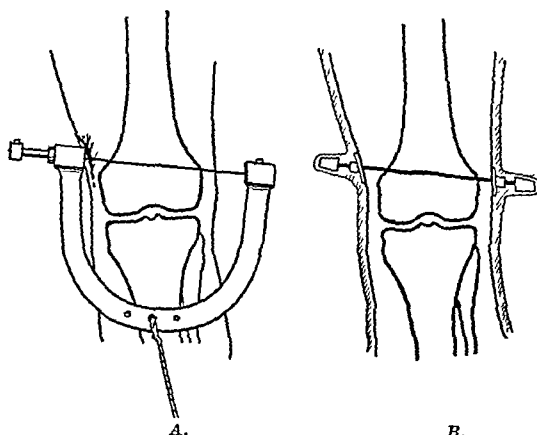


Fig 5—A, Failure to limit side motion between transfixion and bone is productive of complications.

B, A firm binding of the transfixion to the fragment is essential for success. Incorporation of the pin forestalls contamination from the patient's fingers, holds the reduction, eliminates infection from sidewise slipping, and avoids all pain. If location of fracture and associated wounds permits, it is better to insert angularly two transfixions into each fragment.

finger or stick. With this type of patient it is well to cover transfixion areas with large dressings or with a segment of plaster cast.

*Immobilization of Transfixions.*—Regardless of the location and care with which a wire or pin is inserted, it is evident that subsequent movement of the bone upon the transfixion can but result in a frictional irritation with discharge and pain. Breaks in the technique that result

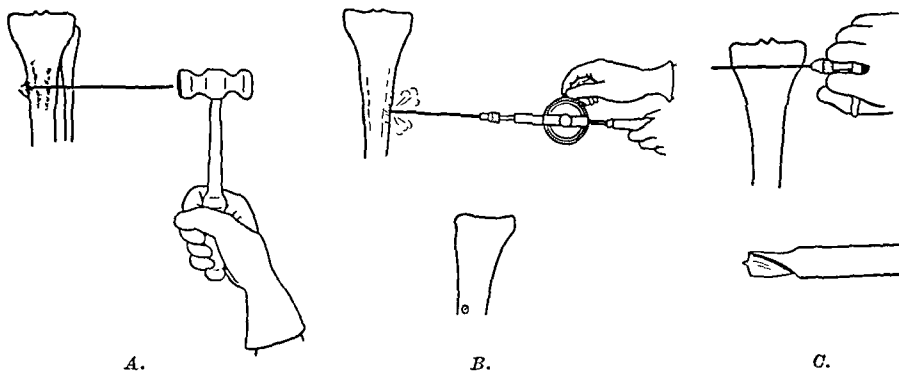


Fig. 3.—A, Why place a pin through bone that is so dense it is necessary to use a hammer? Such an act often further fractures the shaft and explodes the exit hole. A pin so placed is both painful and so loose that accurate reduction cannot be maintained.

B, The placement of pins through dense cortex, use of thick pins with dull points, or excessive haste will cause a thermal necrosis of surrounding bone with a late ring sequestrum.

C, Insertion of pins with special sharpened points at proper locations, and at a slow speed with hand drill or electric motor, avoids most, if not all, cases of aseptic thermal necrosis which have been erroneously termed infection.

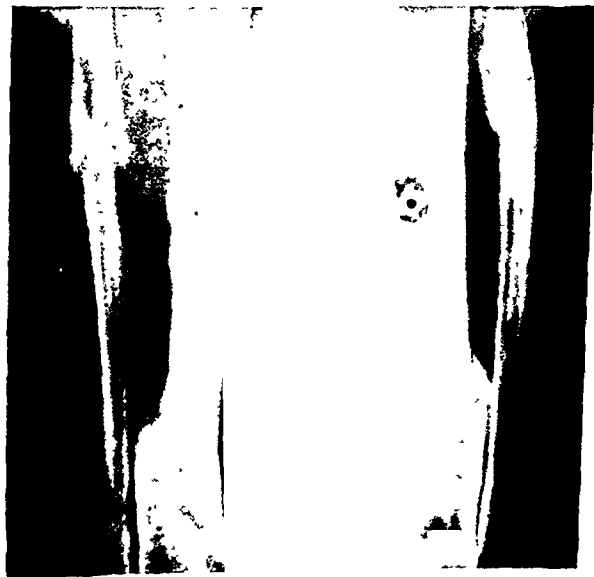


Fig. 3D.—Improper placement of the pin through the crest of the tibia resulted in typical ring sequestrum. The eradication of this sequel required more time, expense, and pain than the original fracture.



Fig. 7A.—If half-pins do not penetrate beyond the opposite cortex, movement with pain and loss of apposition will occur.

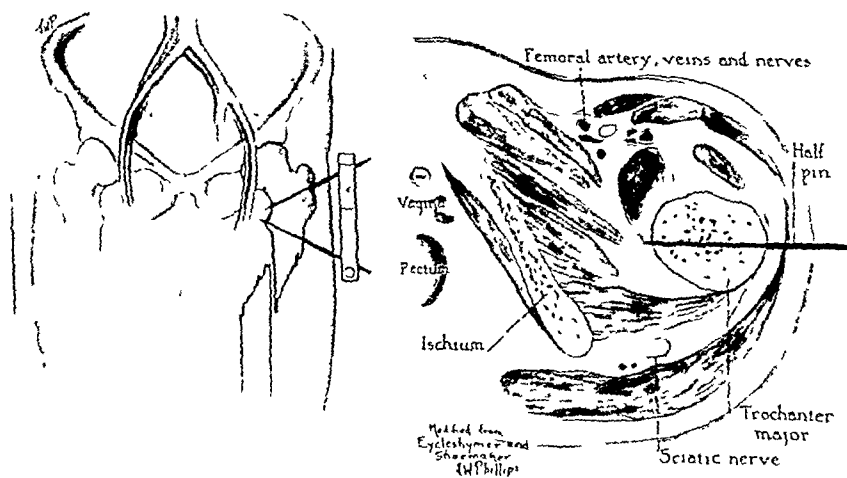


Fig. 7B.—Half-pins may penetrate safely the opposite cortex of any shaft fracture as every fragment has a practical and safe portal of entry.



2. Employment of a lax wire through use of an inadequate horseshoe or reliance upon the sides of the cast to keep the flexible transfixion taut.
3. Improper placement of a transfixion through an adjacent bone rather than through the fragment itself.
4. Insistence on hammering the transfixion through the bone, in which event an enlarged opening is often "exploded" in the opposite cortex.
5. Needless fear of injuring deeper structures leads to the selection of too small a half-pin unit or to incomplete penetration of the opposite cortex with the half-pin.
6. Failure to employ an adequate number of transfixions is the error productive of most complications.

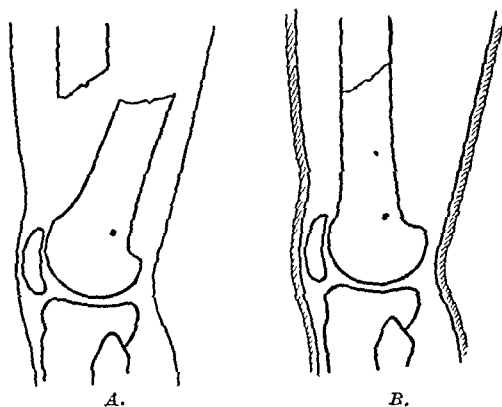


Fig. 6.—A, It is impracticable to control the deformity in a supracondylar fracture by single transfixion as the fragment is free to pivot on a single pin.

B, Double transfixions supply means of "freezing" this fragment in one position throughout convalescence. Paradoxical as it may seem it is much safer to employ several than a single transfixion.

Paradoxical as it may seem, it is safer to use several rather than a single transfixion. The fragment encased in a cast can pivot or teeter-totter on a single transfixion, and as atrophy occurs and the swelling recedes the bone may slide sidewise in the cast; whereas, if two or more pins, wires, or half-pins are placed at an angle to each other, movement of the fragment on the transfixions is impossible.

It is an absolute necessity for half-pin transfixions to go through both cortices if subsequent movement is to be avoided; yet in the use of our half-pin unit a not infrequent cause of undesirable sequelae is failure to drill through the opposite cortex. Penetration of a single cortex not only fails to fasten the pins securely into the bone but subsequent movement of the bone on the pin will often cause pain, discharge, and loss of reduction.

*Control of the Forces Available Through Transfixation.*—For earliest possible union it is necessary for the fragments to be immobilized in direct contact during the entire healing process. Throughout the convalescence period absorption occurs at the ends of the fracture fragments. This is especially evident in transverse fractures in the distal



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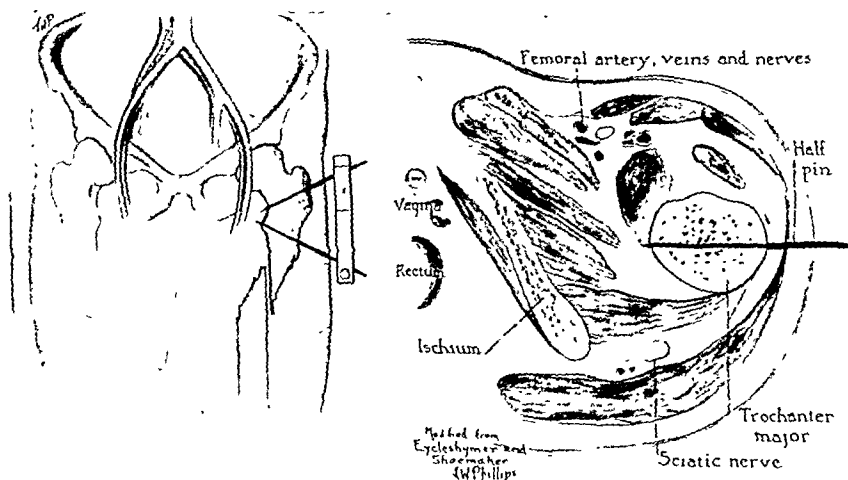


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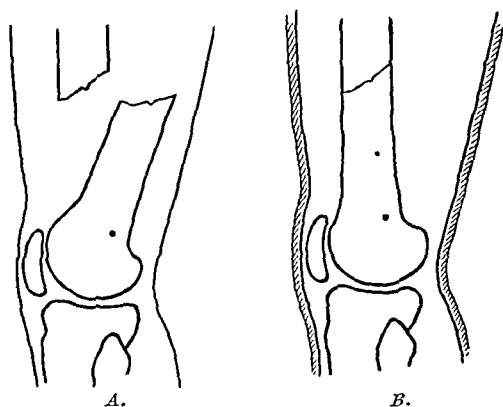


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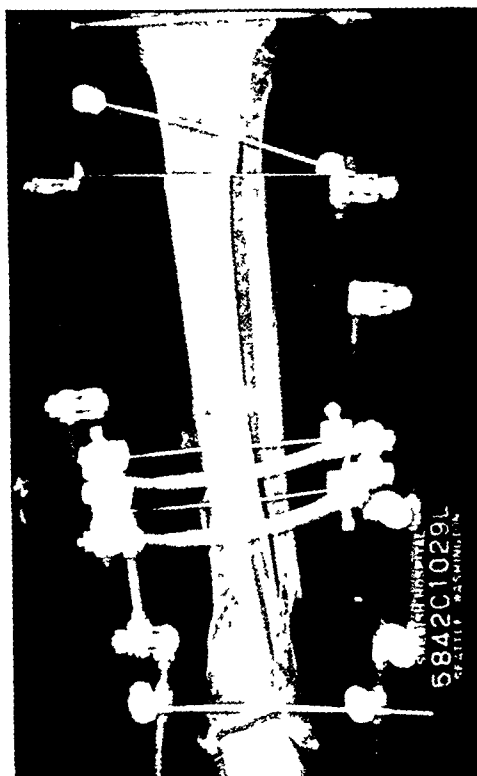


Fig. 9A.—The quickest method ever devised of obtaining union is by "contaction" procured through double transfixation of each fragment. In this print the films have been spliced together to show two transfixations in the upper fragment and two Kirschner wires in central fragment. There was room for only one pin in the distal fragment. The angle in which the x-ray was taken makes it appear that the pin was in the ankle joint.

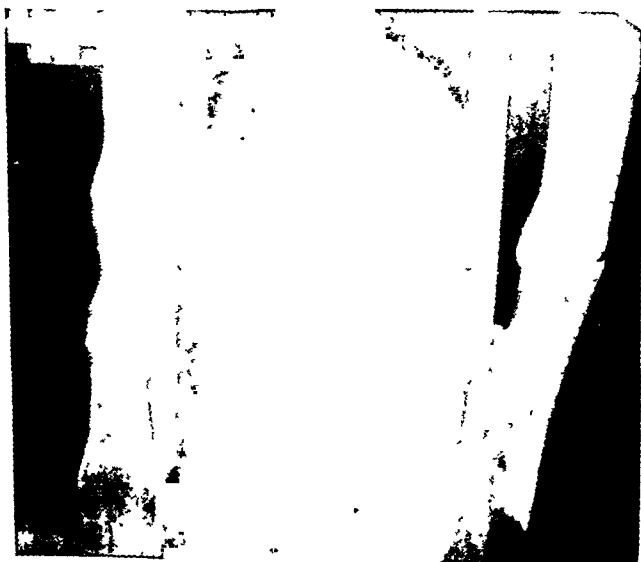


Fig. 9B.—Final result, four months later.

one-third of the tibia. This bony absorption, which we attribute to trauma of the osseous-vascular system, is not visible for several weeks or months. Therefore, transfixions which at first hold the fragments in perfect apposition may be, in transverse fractures, the same means that will hold the fragments apart after absorption has taken place.



Fig. 8.—A, The surest way of obtaining nonunion is to immobilize the fragments in distraction.

B, X-ray of the same patient eighteen months later when he first came under our care. In spite of a sliding bone graft, nonunion has persisted, partially accounted for by the distraction of a united fibula.

Before the days of modern fracture treatment, malunion was a common complication; but the thoughtless and enthusiastic employment of skeletal distraction has now reversed the trend and placed that greater catastrophe, nonunion, in the ascendency, well explained on the basis of overextension. However, when these same transfixions are used in the reverse manner (i.e., for "contaction") then and only then can unions be obtained in the shortest possible time.

Failure to keep a patient ambulatory, now feasible with our newer knowledge of transfixation, provokes a long train of undesirable sequelae such as stiff joints, muscle and bone atrophy, circulatory atresia, edema,

## RESECTION OF FEMORAL NECK WITH PELVIC SUPPORT OSTEOTOMY FOR ANKYLOSIS OF THE HIP

HENRY MILCH, M.D., NEW YORK, N. Y.

THE therapy of ankylosing affections of the hip has swayed between a natural desire to achieve painless stability and a laudable wish to preserve or restore painless mobility. The result is that the orthopedic surgeon has employed his utmost energies in perfecting methods for insuring firm fusion of the hip joint and then equally determinedly devised the most ingenious techniques for undoing the ankylosis which may present itself. This apparent inconsistency is readily comprehensible and would be completely justifiable were there any assurance of success, either in the arthrodesing or in the arthrolysing procedures. Such is not the case and it is this inadequacy which may possibly condone the following presentation.

Essentially, the method here suggested is a combination of two separate surgical procedures. The first, designed to preserve stability by making a new point of pelvic support other than the femoral head, is accomplished by means of the Lorenz bifurcation osteotomy. The second, directed toward the re-establishment of mobility, is accomplished by a modification of the pseudo-arthritis principle recommended by Jones. As a matter of fact, the operative approach was a natural development of the treatment of the fractured neck of the femur. It is of considerable interest to recall that the bifurcation operation suggested by Lorenz was originally the result of his observations of a war-incurred fracture of the upper end of the femur. Subsequently, the bifurcation was successfully employed routinely in the treatment of nonunited fractures of the femora. It was as a consequence of the satisfactory results in the care of this condition that Dr. H. Finkelstein suggested the conversion of the ankylosed hip into a pseudo-arthritis, which could then be stabilized by means of the pelvic support osteotomy.

The first of these operations was performed in 1934. Since that time some seven or eight other hips have been similarly treated. The results have not been uniformly good. But in certain types of cases where the need for mobilization of the ankylosed hip has been urgent, and where the advisability of a formal arthroplasty was questionable, the operation has proved of value. This is illustrated in the case here reported.

C. K., aged 10 years, first came to the Hospital for Joint Diseases, March, 1928, with the complaint of pain and swelling in the left knee joint. These symptoms appeared following an injury some two months before. The mother stated that at the age of twenty-six months the child had been treated at the Ruptured and Crippled Hospital for a left hip limp, of nine months' duration. An abscess of the left

and general metabolic and psychic changes. In order that these be reduced to a minimum, it is highly desirable that ambulation and active joint movement be insisted upon. Improved vascular and lymphatic circulation, through function and muscular contraction, decreases the swelling, and ambulation prevents marked muscle and bone atrophy and joint stiffness. With an increased active blood and lymph flow it is axiomatic that more callus and union in less time is not only possible but probable.



Fig. 10.—A. I., aged 28 years, with fractured shaft of the femur. The psychologic, physiologic, and economic benefits of early ambulation with free joint movement are numerous.

*Prophylaxis.*—Complications, as a class, are avoidable and may be limited to a minimum approaching zero when the following technique is carefully employed. Insert transfixions, whenever possible, through the wide cancellous portion of the bone. Place two pins, two wires, or two half-pins at an angle to each other into each fragment. Use the transfixions for traction only in reduction; then reverse the procedure and use the transfixions, for a "contactation" means to keep the ends of the fragments in direct and immobilized contact throughout the whole period of repair. Employment of the above clinically tested principles, and insistence on ambulation with active muscular and joint movements, will be rewarded by an earlier bony union than can be attained by any other method.

#### RÉSUMÉ

Sequelae are usually due not to use but to misuse of transfixation. The common errors causing the majority of complications, arising from fear, unpreparedness, or haste, may be classified under (1) improper placement; (2) movement between fragment and transfixion; (3) use of transfixions for skeletal traction instead of contactation; and (4) failure to use transfixions so that the benefits of ambulation can be realized.

success. The indication for surgical fusion of the knee joint appeared to be urgent. On the other hand, the already existing fusion of the hip joint seemed to present an equally formal contraindication to a second fusion in the same limb. The only solution to the dilemma lay in a release of the hip before proceeding with ankylosis of the knee.



Fig. 1.—Roentgenogram (C. K.) showing that the joint space has been obliterated, but the remnants of the head are still to be seen. In the region of the epiphyseal line, there is a zone of radiotranslucency.

At that time the bifurcation resection operation was being developed and it was determined to employ this in preference to a more standard type of arthroplasty. This was a purely fortuitous, but entirely fortunate decision, as the event proved. On Nov. 12, 1937, the hip joint was approached through an anterior Smith-Petersen incision. The ankylosis was released by an osteotomy performed on the neck, close to and parallel with the pelvic wall. No effort was made to gouge the head out of the acetabulum. This released the femur, but to prevent the possibility of re-ankylosis, the whole of the neck down to its base was excised in a single piece. No tissue was interposed and the wound was closed in layers. The knee was immobilized in plaster.

As a matter of routine, the specimen was submitted to histologic examination. Microscopic section disclosed "the spongy trabeculae to be atrophic and the cortex thin. Almost at the center of the section is a caseous, partly calcified mass. It is surrounded by a collar of epithelioid cells and collagenous connective cells. About



thigh was incised and drained. Traction was applied and subsequently the thigh was immobilized in a plaster of Paris spica. No definite bacteriologic diagnosis was established, though tuberculosis was undoubtedly suspected, since the immobilization was continued for a period of four years. Upon removal of the plaster, the symptoms had disappeared, but the child was left with a marked limp, due to ankylosis of the hip in adduction and flexion.

On admission to the hospital, the left hip was fixed in 10 degrees of adduction and about 30 degrees of flexion. There was no active motion, but the suspicion of a very slight amount of external rotation on passive motion presented. The roentgenogram was reported as showing a destructive arthritis of the hip joint, with bony ankylosis. The knee joint was palpably the site of a marked effusion. Extension of the leg was limited. Roentgenogram of the knee joint showed no bony changes. The Wassermann test was negative, but the intradermal tuberculin test was positive in all dilutions. Fluid aspirated from the knee was sterile on ordinary culture. (Guinea pig inoculation was subsequently reported to be negative.) A diagnosis of nonspecific synovitis of the knee was made, as previously it had been made elsewhere, with respect to the hip. The knee was immobilized in a plaster of Paris mould. In May, 1928, the child was discharged to the outpatient department.

Under conservative treatment, the acute manifestations subsided. The child remained relatively free of symptoms until May, 1931, when she was again admitted to the hospital for pain and swelling of the knee. At this time it was noted that slight rotation was present in the hip and doubt as to the nature of the ankylosis was expressed. The roentgenogram (Fig. 1) was reported as showing an old ankylosing process of the left hip. However, later restudy disclosed that the head and neck were absorbed, that the joint space was completely obliterated, but that below the femoral head, in the region of the epiphyseal line, there was an irregular zone of radiotranslucency, similar to that which has since been seen in cases of epiphyseal pseudo-arthritis.<sup>1</sup>

Though the specific therapy of this condition was not at that time recognized, a pelvic support osteotomy was performed, but for other reasons. Because of the necessity for immobilization of the knee, it was decided to correct the hip deformity at the same time and so save the patient unnecessary hospitalization. On May 15, 1931, a subtrochanteric osteotomy was attempted. The distal fragment, however, became displaced medially, so that in effect a Lorenz bifurcation was performed. Specimen of the bone removed at the time of operation showed no evidence of any tuberculosis. The convalescence was uneventful, and in June the patient was discharged in a plaster of Paris spica. In September, the plaster was removed and the patient was permitted to bear weight on the affected limb. Physiotherapy was instituted as soon as the patient's pain subsided.

Following her discharge from the hospital, the patient made intermittent visits to the dispensary. In 1936, roentgenogram revealed a destructive lesion in the external condyle of the left femur, which was considered to be tuberculosis. The pain gradually became worse, so that in October, 1937, the patient could no longer bear weight upon the knee joint. She was immobilized in plaster and advised bed rest, but without relief of symptoms. In November, hospitalization was advised. At this time the knee was found swollen, tender, and warm to the touch. There was a moderate valgus, which was attributed partly to the tuberculosis and partly to the antecedent bifurcation operation. Motion at the knee was limited to 155-degree extension and 100-degree flexion. The hip was solidly fused and painless (Fig. 2).

The patient now presented an extremely disturbing problem. She was 19 years of age and was suffering from what was clinically tuberculosis of the left knee. This had been treated conservatively for a period of about nine years, but without

and could sit down. Even though she had but little active power in the hip muscles and walked with a limp, she had a remarkably stable and painless hip. Roentgenogram of the hip taken at this time (Fig. 3) was reported as showing "a firmly united bifurcation osteotomy of the femur, with the upper end of the distal fragment forming a new joint between it and the base of the ascending ramus of the pubic bone close to the acetabular ring."



Fig. 3.—The femoral neck has been resected and motion restored. Stability is maintained by pelvic abutment of the apex of the postosteotomy angle.

This position is of course not ideal for the re-establishment of physiologic motion. In fact, it may be one of the factors responsible for the inability actively to move the limb. On the other hand, the limitation of active motion may be due to intrinsic loss of power in the muscles themselves. All too frequently sight is lost of the fact that mere reconstruction of the mechanical conditions for motion does not assure the result, unless some means of restoration of the motor power, that is of the re-establishment of the biomechanics of the joint, is guaranteed. In a patient such as has been described here, where passive motion far exceeded the range of active motion, it must be presumed that the muscle motors had been damaged beyond repair by the antecedent inflammatory

this is a zone of lymphocytes and plasma cells, in which collections of epithelioid and giant cells may be observed.

“*Diagnosis.*—Tuberculoma of the neck of the femur, in a case of old, healed tuberculosis of the hip joint.”

Motion of the hip was started ten days after operation and walking with the aid of crutches was permitted at the end of six weeks. The patient left the hospital on Jan. 1, 1938. In July, 1938, the range of motion at the hip included flexion from 170 to 145 degrees, external rotation 5 degrees, adduction 15 degrees from the midposition, and abduction 5 degrees from the midposition. Actively, the patient was able to raise the leg from the examining table, even though she was wearing a Thomas walking brace to protect the knee.

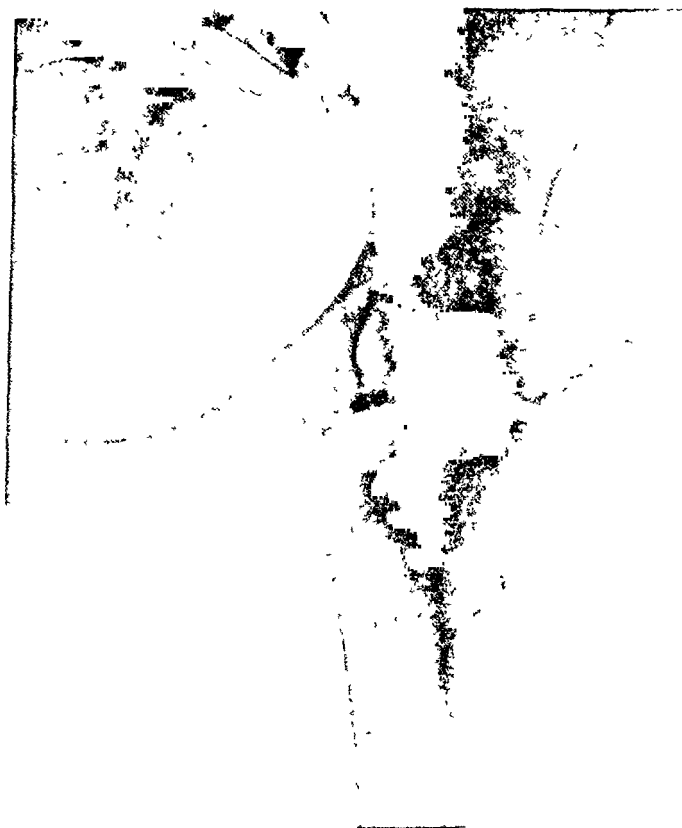


Fig. 2.—The hip is solidly fused; the characteristics of the Lorenz bifurcation have disappeared and the femur presents the appearance of a Schanz type of pelvic support osteotomy.

Examination in April, 1940, revealed essentially the same arcs of passive motion, without any increase in active power. The knee joint was flexed at 145 degrees and roentgenogram of the knee joint disclosed destruction of the lateral femoral condyle. “There is very little motion at the knee and the process appears to be slowly progressing.” Admission to the hospital for fusion of the knee was recommended, but was refused by the patient, because of the subsidence of acute symptoms. The patient was seen again in May, 1941. The conditions in the hip were essentially unchanged. The patient was able to get about with moderate comfort

be instituted as after any other arthrolysis. But, contrary to the practice in other arthroplasties, weight bearing may be permitted as soon as the postoperative reaction has subsided.

#### SUMMARY

An operative procedure for the treatment of hip ankylosis is presented. In principle, the operation consists of two separate operations performed in successive steps: the first stage, the Lorenz bifurcation osteotomy, undertaken in order to insure stability of the hip; the second stage, release of the hip by resection of the femoral neck or head, is performed when bony union following the osteotomy has occurred. This combination affords the opportunity of satisfying both primary requirements of hip function, stability and mobility. It can be employed in cases where the classical types of arthroplasty cannot be employed. The operation is relatively free of shock, and can be carried out at intervals that require relatively short periods of enforced hospitalization. Each of the steps in the operation is simple and does necessitate the refinements of organization that formal arthroplasty makes essential.

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process and by the subsequent prolonged immobilization during the period of fusion. This objection applies to all types of arthrolysing operations, quite irrespective of the mechanical efficiency of the joint which may be the result of the surgical intervention.

Whether the surgical effort in any particular case should be directed toward the remodeling of a new anatomic hip joint, or merely toward release of the ankylosis, will be largely a question of individual preference or experience. The startling discovery of a tuberculoma of the neck in the case here reported suggests the possibility of a disastrous reactivation of the process, had the usual type of arthroplasty been performed. On the other hand, the uneventful response following resection of the neck would appear to speak in favor of the procedure in these types of cases. It would seem to have its special field of usefulness in those cases in which the absence of a femoral neck would preclude the performance of the usual type of arthroplasty.

A further advantage of the operation is that it is performed in two stages, neither of which is shocking to the patient. The operation has been performed at one sitting, but this is considered inadvisable, since the plaster immobilization necessitated by the osteotomy prevents the mobilization which is desirable after release of the ankylosis. At the outset, the effort was made to mobilize the hip before attempting osteotomy of the shaft. While this materially reduces the technical obstacles, some difficulty was experienced in the prevention of upward displacement of the shaft between the first and second stages. At present, osteotomy is performed as the first stage. This may be done simply through a small, lateral incision, at the base of the trochanter, or may be performed with greater precision through an anterolateral incision, which permits accurate displacement of the distal fragment. Following abduction of the osteotomized fragment, both hips are immobilized in plaster, until firm bony union has taken place. In performing the abduction, no attention need be paid to the size of the postosteotomy angle.<sup>2</sup> Since the head and neck are to be removed, the pelvis will be supported by only a single fulcrum at which no limitation of motion can occur. Nevertheless, excessive abduction is to be avoided and 30 degrees may be taken as an average maximum of abduction for the distal fragment.

Following re-establishment of bony continuity at the site of the pelvic support osteotomy, the second stage for release of the ankylosed head is undertaken. If the head can be easily separated from the acetabulum, it may be exenterated and removed in one piece with the neck, which should be cut through at its base. If, however, the ankylosis is so solid that the head cannot be easily delimited, no effort should be made to gouge out the acetabulum, after osteotomy at the base of the neck. The femoral head should be released by another osteotomy made flush with the pelvic wall. Traction and graded active and passive motion should

# DOUBLE PULLEY HUMERAL ADAPTATION OF RUSSELL TRACTION

DONALD W. SMITH, M.D., MIAMI, FLA.

**I**N TREATING fractures of the shaft of the humerus many methods are available, depending upon the type of fracture, its location, associated injuries, and the surgeon's experience and ability. In the hands of an expert the frequent election of open reduction may produce gratifying results, whereas its general use may be disappointing. The immediate application of a cast, with or without some form of ambulatory traction, has its place in selected cases but frequently a better immediate and final result with a shorter ultimate period of incapacity and, as Colp and Findlay<sup>1</sup> have shown, a quicker economic restoration may follow hospitalization with extension.

There are many indications for caution in the employment of the bedside extension methods. Speed<sup>2</sup> has recently emphasized the fact that the most frequent error committed is "overpull" with resulting interposition of soft parts or periosteum, preventing reapposition and frequently resulting in delayed or nonunion. Inadequate traction or loss of traction, through errors in application of the equipment or arrangement of pulleys, and inadequate nursing care may cause over-riding or malalignment.

Certain complications common to the various methods of application may also occur. The use of too much weight may cause adhesive to slip and injure the skin, resulting in infections which interfere with subsequent operations.

As Heyl<sup>3</sup> has pointed out, skeletal application of traction permits the use of greater weights and skin injuries are avoided. It must be remembered, however, that every wire, nail, or tong causes a compound injury to the bone and carries with it the hazards associated with that type of injury. Mathewson<sup>4</sup> calls attention to the fact that incorrect angle, avulsion, bending or slipping of the wire or nail, injury to nerves and blood vessels, pressure necrosis or gangrene of soft parts, hematoma formation, and infection of the skin or bone are occasionally encountered when skeletal traction is employed.

The system most commonly used in applying traction to the humerus consists of two or three separate weight and pulley combinations as presented in 1918, by Blake and Bulkey,<sup>5</sup> one pulling through an overhead pulley on a Balkan frame to a hand spreader, another through a pulley on a traction stand for lateral traction of the humerus, and a third, through a pulley on the Balkan frame to a sling under the humerus.

This multiple weight system requires considerable care in its application, constant observation, and frequent adjustments. A further disadvantage is the inability of the patient to change position in bed. The necessity of maintaining a flat supine position for about six weeks or until some bony union has resulted creates a definite nursing problem and causes the patient a great deal of discomfort.

Certain modifications of pulley arrangement such as that described by Blum<sup>6</sup> have simplified and improved this system of traction but without simplifying the nursing problems presented by the bedridden patient.

Herewith, we present a new and simple method for the application of traction which will permit the patient to assume a lying or sitting position in bed, thus simplifying the nursing care. The following is not a description of a new apparatus, but of a physiologically correct axis traction adaptation for use in selected fractures of the shaft of the humerus in which hospitalization is indicated.

#### ADAPTATION

The patient is placed in bed with the emergency Thomas splint in place and the traction is applied without altering the position of fragments as revealed by roentgenogram upon admission.

A Balkan frame is placed on the bed and a single pulley is attached to an overhead extension arm which is adjusted to allow the desired degree of abduction and flexion. The usual type of hand cage or spreader is applied by adhesive strips to the dorsal and volar surfaces of the forearm. A spreader with one double or two single pulleys attached is fastened to the antecubital region by a felt sling or by mole-skin or adhesive tape. In the latter case the tender medial aspect of the arm is avoided. The adhesive strip is attached posteriorly and is passed outward over the spreader where it is divided and faced, each half passing about the forearm without adhering until, as it encircles the arm, it reaches the tape posteriorly.

The rope attached to the hand spreader is passed through the pulley on the overhead extension arm of the Balkan frame in order to support the forearm. From there it is passed through one-half of the double pulley system at the elbow, then through a single pulley attached to the end of the Thomas splint and, finally, through the other pulley at the elbow down to the weight below. In this way lateral traction and countertraction are produced to maintain humeral extension.

The pulley arrangement is shown in Fig. 1. In Fig. 2 is shown a superimposed parallelogram of forces with  $OA$  extending from the elbow toward the single overhead pulley. This force equals that of the suspended weight. The force  $OB$ , from the elbow through the double pulley system laterally, equals twice the suspended weight. When deducting the weight of the forearm and hand cage it is found that about three-fourths of the suspending force  $OA$  has been neutralized leaving  $OA'$  as the force entering into the parallelogram of forces act-

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ing at the elbow. The resultant  $OX$ , slightly greater than  $OB$ , is found to lie in the axis of the shaft of the humerus.

A three-pound weight exerting its traction through the single overhead pulley will produce a three-pound lift to support the arm and hardware, and through the double pulley system, it will produce slightly more than a six-pound extension traction upon the fracture site.

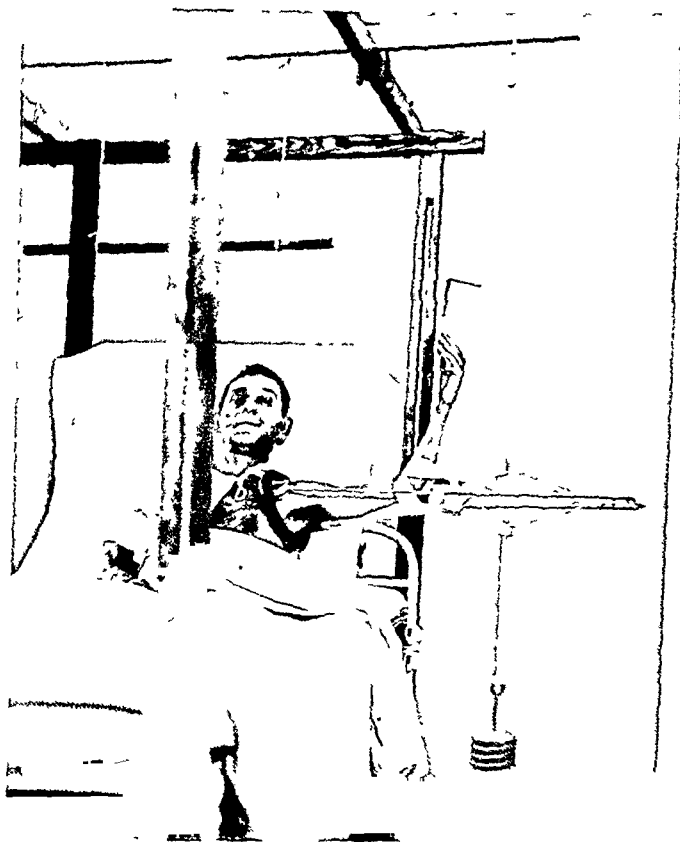


Fig. 1.—Double pulley traction method of humeral extension in fractures of the shaft of the humerus, showing application and pulley arrangement. Bandage and humeral sling are omitted for purpose of illustration. Lowering of back rest will allow patient and apparatus to descend. The rope travels through the pulley system as the weight is raised.

It has been found that arms requiring more or less traction also require a correspondingly heavier or lighter weight for their support. By using weights from two to six pounds this system is, therefore, applicable to children as well as to muscular adults. To decrease or increase the lift on the forearm the overhead pulley may be shifted outward or inward, thereby increasing or diminishing the resultant forces involved in lateral traction. A much simpler method, however, is to lock the overhead pulley in the desired position by means of a plug or clamp.

A muslin sling may be fastened over the bars of the Thomas splint to support the humerus. It may become necessary to support the splint with tape applied to the forearm or with rope attached to or above the hand spreader.

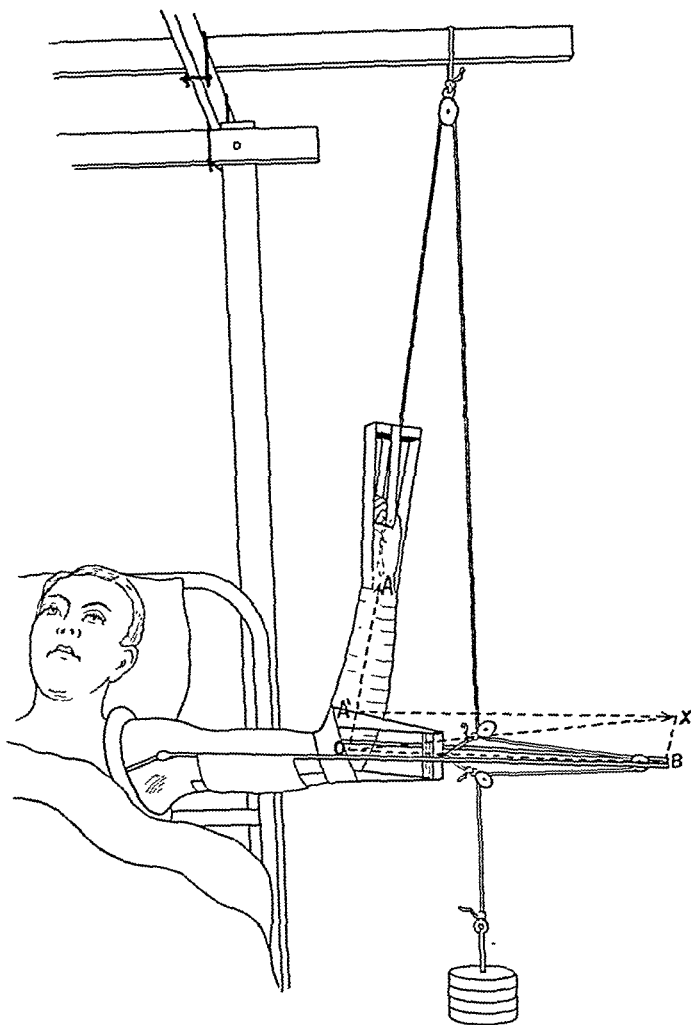


Fig. 2.—Illustration showing superimposed parallelogram of forces.  $OA$ , Equals that of the suspended weight;  $OB$ , acting through the double pulley system, equals twice the suspended weight.  $O.I'$  is the portion of  $OA$  entering into the parallelogram of forces ( $A'A$  being neutralized by the weight of the arm and hand cage).  $OX$ , the resultant of forces  $OA'$  and  $OB$ , lies in the axis of the humerus.

When the adjustments are all made, the outstanding advantage of this system over other methods of extension becomes apparent. As the patient rises on the back rest, the nurse gently lifts the end of the Thomas splint and the rope travels through the system of pulleys as the weight descends. Merely lifting the weight allows the arm and splint to descend as the back rest is again lowered.

## ADVANTAGES

1. No special equipment is required.
2. It is comfortable and it may be adjusted with ease; no angle calculations are necessary.
3. No tilting of the bed is required; there is no loss of traction caused by the elbow spreader striking the pulleys as there may be with the usual traction stand.
4. Less supervision is required by the nursing staff.
5. There is no posterior angulation of the fracture when the patient is raised from the mattress for the usual nursing care; the sling attached to the Thomas splint rises with the extension system.
6. The patient may be readily transferred from Thomas splint emergency traction; he may be safely transported to the x-ray department for studies when portable equipment is not available.
7. This system is adapted to skeletal traction by means of a wire through the distal humerus or olecranon, or to modifications of skin traction as advocated by Blum<sup>6</sup> and Butcher.<sup>7</sup>
8. There is less force exerted upon the arm for corresponding amount of axis traction than in other forms of multiple pulley systems, such as that described by Blum,<sup>6</sup> as there are no widely separated opposing forces producing a resultant. The single pulley force overhead is practically equalized by the weight of the arm and hardware, while the greater, double pulley force corresponds with the desired axis for humeral traction.
9. The freedom of motion afforded makes the patient's hospitalization much more bearable.

## SUMMARY AND CONCLUSIONS

Some of the common methods of management of fractures of the distal half of the shaft of the humerus are mentioned with comments on the deficiencies of the existing methods of bedside traction systems.

A new double pulley method of humeral extension is described which eliminates many of these deficiencies and provides certain advantages which other extension methods do not offer.

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# INTESTINAL ACTIVITY FOLLOWING DISTENTION OF THE GALL BLADDER AND URINARY TRACT: AN EXPERIMENTAL STUDY\*

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THE gastrointestinal manifestations accompanying diseases of the biliary tract or of the urinary tract are well known. In many cases these diseases are accompanied by some transitory or permanent gastrointestinal symptom, that is, nausea, vomiting, epigastric distress, abdominal discomfort, ileus, distention, constipation, and so forth. These secondary symptoms are at times so conspicuous as to cloud the true nature of the primary disturbance and to lead to an incorrect diagnosis. A possible explanation of some of the symptoms noted clinically in these cases may be found in recent experimental work in this field of research. To date this has dealt mainly with the stomach but we shall concern ourselves only with the effect of distention of the gall bladder or of the urinary tract on the small intestine.

Schrager and Ivy found that when the gall bladder of the dog was distended by inflating a toy balloon placed in its lumen, the animal experienced discomfort and occasionally salivation and vomiting. Distention of the biliary ducts caused marked discomfort; pressures of more than 100 mm. of mercury always produced salivation and frequently produced vomiting. It was evident that the symptoms were more intense and uniform when the biliary ducts were distended than when the gall bladder was distended, and the symptoms could be elicited with less pressure.

Zollinger performed similar studies on man. The gall bladder and the common duct were distended after the patient had recovered sufficiently from a short period of anesthesia to answer questions intelligently. Distention of the gall bladder did not cause vomiting, whereas distention of the common duct frequently did cause vomiting.

Welch, Coplan, and Holmes stated that roentgenoscopic observations on the duodenum and jejunum of patients who had pathologic changes in the ureter indicated that there are spasm of the duodenal cap and hyperperistalsis of the descending loop of the duodenum, sometimes so severe as to cause regurgitation.

King inserted a cannula through the apex of the bladder of barbitalized dogs, so that the bladder could be filled or emptied at will by raising or lowering a pressure bottle connected to the cannula in the bladder. Intestinal records were made with a balloon-tambour system.

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He found that when the pressure bottle was raised very slowly, no change of duodenal activity took place. The response to sudden and rapid increase of pressure was somewhat variable, but quantitative rather than qualitative. King never observed any augmentation of duodenal tonus and movements under these conditions, but quite constantly he observed a diminution. In many of his cases the relaxation was small, in others it was prompt and complete.

The objective of the investigation reported here was to determine if changes in the activity of the jejunum and ileum could be produced by distention of (1) the gall bladder, (2) the upper part of the urinary tract, or (3) the urinary bladder.

#### METHOD OF STUDY

Female dogs, weighing between 8 and 17 kg., were used in these experiments. All the animals were trained for making the necessary observations and recordings. All operative procedures were made with the animal under ether anesthesia, using surgical technique. Studies were not done until healing had occurred. Advantage was taken of the technique devised in this laboratory<sup>3</sup> for obtaining samples of intestinal contents and used subsequently for the study of intestinal peristalsis.<sup>7</sup> This preparation consists of a loop of small intestine in continuity with the remainder of the bowel, with blood and nerve supply intact, enclosed in a bipedieled loop of skin. Records of intestinal activity were obtained by means of a double tambour system, the receiving tambour being fastened to the loops of intestine by an aluminum clip, and the recording tambour being attached to a recording lever, the excursions of which were recorded on the kymograph.

*Distention of the Gall Bladder.*—Distention of the gall bladder was accomplished by inflating a fine rubber balloon which had been inserted through the fundus into the lumen of the gall bladder. The balloon had been tied previously over the end of a size 16 self-retaining catheter in such a way that when it was filled without tension it was of approximately the same size as the cavity of the gall bladder. The opening in the fundus was closed securely around the catheter, which was brought to the outside through a stab wound. The gall bladder was distended by injection of saline solution at the body temperature of the animal (39 to 40° C.) from a syringe into the catheter-balloon system in the gall bladder. The catheter was fitted with a glass T tube, to provide for the inclusion in the system of a simple mercury manometer. In this way the gall bladder could be distended slowly or rapidly to whatever pressure was desired and this pressure could be maintained for whatever period was desired. The distention was maintained usually for fifty to sixty seconds and an interval of several minutes elapsed between successive trials.

The experiment was first done on the animals recently fed and was repeated after a twenty-four- to forty-eight-hour fast. In this manner, the effect of distention of the gall bladder was studied in all phases of

intestinal activity, from the vigorous, steady activity in the recently fed animal to the infrequent, feeble, and irregular contractions which interrupt long periods of quiescence in the fasted animal.

*Distention of the Upper Part of the Urinary Tract.*—Distention of the upper part of the urinary tract was accomplished by injecting water or dilute urine through a ureteral catheter. The details of technique in the procedure of ureteral catheterization have been worked out by Greene and his method was used. The animal was anesthetized with pentothal sodium administered intravenously. A 5 per cent solution was injected at a rate of about 1 c.c. per minute. From 4 to 6 c.c., depending on the size of the animal, were necessary to induce a stage of anesthesia suitable for work with the cystoscope. The animal was maintained at this level by the injection of 0.5 to 1 c.c. of the anesthetic agent from time to time as necessary. Intravenously administered pentothal sodium is very satisfactory for this work, because the animal wakes within one-half hour after administration of the anesthetic agent has been discontinued and completely recovers within two hours. There is very little vomiting or other gastrointestinal disturbance, and the animal will eat shortly after waking.

With the animal under anesthesia as described, the urethra was dilated to a caliber of 28 French with van Buren sounds. A 24 French Braasch cystoscope then could be introduced readily into the bladder. The ureteral orifices were identified and a suitably sized ureteral catheter (5 or 6 French) was manipulated through the ureterovesical valve of the more easily accessible ureteral orifice and passed on up into the pelvis of the kidney. The cystoscope then was removed, the catheter being left in place and fixed with adhesive tape to the perineum. An attempt was made throughout the procedure to maintain sterile technique.

The presence of the catheter in the ureter did not disturb the animal to any discernible degree, and once the animal had recovered completely from the anesthetic, it appeared normal in every respect. The animal was fed twenty to thirty minutes before the start of the experiment to insure active peristalsis during the study.

With the trained animal tied on the padded frame, water or human urine at 39° C. was injected from a syringe into the ureteral catheter. In several of the experiments, the catheter was pulled down 8 to 10 cm. after studies had been made with the tip of the catheter in the renal pelvis, and the experiment was repeated with the tip of the catheter in this lower position. The length of the ureter in the dog as determined from post-mortem studies varies according to the size of the animal; in animals of the size studied (12 to 16 kg. respectively) the ureter was found to be about 22 to 25 cm. in length.

Each subsequent catheterization was performed on the same animal after an interval of two to three weeks. In this interval of time between catheterizations, the trauma and edema resulting from the procedure had subsided and the bladder and ureteral orifices, as seen through the

He found that when the pressure bottle was raised very slowly, no change of duodenal activity took place. The response to sudden and rapid increase of pressure was somewhat variable, but quantitative rather than qualitative. King never observed any augmentation of duodenal tonus and movements under these conditions, but quite constantly he observed a diminution. In many of his cases the relaxation was small, in others it was prompt and complete.

The objective of the investigation reported here was to determine if changes in the activity of the jejunum and ileum could be produced by distention of (1) the gall bladder, (2) the upper part of the urinary tract, or (3) the urinary bladder.

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Female dogs, weighing between 8 and 17 kg., were used in these experiments. All the animals were trained for making the necessary observations and recordings. All operative procedures were made with the animal under ether anesthesia, using surgical technique. Studies were not done until healing had occurred. Advantage was taken of the technique devised in this laboratory<sup>3</sup> for obtaining samples of intestinal contents and used subsequently for the study of intestinal peristalsis.<sup>7</sup> This preparation consists of a loop of small intestine in continuity with the remainder of the bowel, with blood and nerve supply intact, enclosed in a bipedicle loop of skin. Records of intestinal activity were obtained by means of a double tambour system, the receiving tambour being fastened to the loops of intestine by an aluminum clip, and the recording tambour being attached to a recording lever, the excursions of which were recorded on the kymograph.

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TABLE II

DISTENTION OF UPPER PART OF THE URINARY TRACT:  
DOG 2, LOOP OF ILEUM 10 TO 12 INCHES (25 TO 30 CM.) FROM CECUM\*

DATE	POSITION OF CATHETER TIP	FLUID INJECTED (C.C.)	DURATION OF INJECTION (SEC.)	DURATION OF INHIBITION (SEC.)
3/14/40	Pelvis	6	35	60
		6	20	180
		6	20	150
		6	20	40
		6	20	90
		6	20	60
		6	20	100
		6	20	120
		6	20	90
3/29/40	Pelvis	10	50	50
		10	50	50
		10	25	25
		10	40	70
	10 cm. below pelvis	10	20	20
		10	40	40
		10	30	30
		10	25	30
4/9/40	Pelvis	6	35	65
		10	50	150
		10	50	70
		10	35	55
	10 cm. below pelvis	6	35	180
		10	50	60
		10	50	78
		8	40	120

\*Weight 12 kg., catheter (5 French) in left ureter.

loops of ileum, taken about twelve inches (30 cm.) from the cecum. Twenty-four determinations on different days (eight for each of the three animals) were made on the recently fed animals. In no instance did distention of the gall bladder in the pressure range of 0 to 400 mm. of mercury produce any effect on peristalsis, as observed directly from the loop or recorded on the kymographic record. There was no acceleration or inhibition of the peristaltic waves and no change in tonus, and the essential pattern of the kymographic record was unchanged.

Fifteen determinations on different days (five for each of the three animals) were made on the animals after they had been fasted for twenty-four to forty-eight hours. In these instances the bowel was in a relatively quiescent state with only occasional peristaltic activity. Distention of the gall bladder through the pressure range of 0 to 400 mm. of mercury failed in each instance to stimulate the quiescent bowel.

In 38 per cent of the instances of distention of the gall bladder to pressures of more than 140 mm. of mercury, salivation was noted and in all instances pressures of more than this value produced discomfort. Vomiting did not occur.

*Distention of the Upper Part of the Urinary Tract.*—Distention of the upper part of the urinary tract produced inhibition of activity in both the jejunal and ileal loops (Tables I and II). For the most part, the

TABLE I

DISTENTION OF UPPER PART OF THE URINARY TRACT:

DOG I, LOOP OF JEJUNUM 10 TO 12 INCHES (25 TO 30 CM.) FROM LIGAMENT OF TREITZ  
(WEIGHT, 14 KG.)

DATE	SIZE URETERAL CATHETER (FRENCH)	CATHETER IN RIGHT OR LEFT URETER	POSITION OF CATHETER TIP	FLUID INJECTED (C.C.)	DURATION OF INJECTION (SEC.)	DURATION OF INHIBITION (SEC.)
3/14/40	7	L	Pelvis	8	15	20
				8	20	25
				10	20	25
				10	15	25
				10	40	60
				10	20	35
				10	30	70
3/29/40	6	L	Pelvis	6	40	180
				5	60	210
			8 cm. below pelvis	5	60	300
				8	35	50
				10	60	150
				5	60	90
				6	60	150
				6	30	50*
				7	20	20
			13 cm. below pelvis	6	20	50
				9	40	75
4/22/40	5	R	Pelvis	10	150	150
			8 to 10 cm. below pelvis	20	210	210
				40	300	300
				15	300	0
				10	25	25
				50	120	120
				10	40	90

\*Vomited

cystoscope, appeared normal in every respect. From seven to eleven determinations were made at five-minute intervals on each occasion that the ureteral catheter had been passed.

*Distention of the Urinary Bladder*—This study was performed under the following subdivisions: (a) rapid distention, (b) slow distention, (c) maintenance of inhibition, and (d) exsplantric studies.

In order to fill the bladder, a two-way Robinson latex catheter of suitable size was passed into the bladder and fixed in position with adhesive tape. Water or dilute urine at the body temperature of the animal (39 to 40 °C.) was run into the bladder from a 500 cc. graduated type of the exsplantric apparatus, as described above, at the body of the dog. A Murphy drip was provided for regulation of the flow of the fluid into the bladder. In three of the series, the distention was effected by the use of a 10 cc. syringe, as described above, and in the remaining series by the use of the exsplantric apparatus.

TABLE II

DISTENTION OF UPPER PART OF THE URINARY TRACT:  
Dog 2, LOOP OF ILEUM 10 TO 12 INCHES (25 TO 30 CM.) FROM CECUM\*

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		6	20	150
		6	20	40
		6	20	90
		6	20	60
		6	20	100
		6	20	120
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3/29/40	Pelvis	10	50	50
		10	50	50
		10	25	25
		10	40	70
	10 cm. below pelvis	10	20	20
		10	40	40
		10	30	30
		10	25	30
4/9/40	Pelvis	6	35	65
		10	50	150
		10	50	70
		10	35	55
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		10	50	60
		10	50	78
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\*Weight 12 kg., catheter (5 French) in left ureter.

loops of ileum, taken about twelve inches (30 cm.) from the cecum. Twenty-four determinations on different days (eight for each of the three animals) were made on the recently fed animals. In no instance did distention of the gall bladder in the pressure range of 0 to 400 mm. of mercury produce any effect on peristalsis, as observed directly from the loop or recorded on the kymographic record. There was no acceleration or inhibition of the peristaltic waves and no change in tonus, and the essential pattern of the kymographic record was unchanged.

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*Distention of the Upper Part of the Urinary Tract.*—Distention of the upper part of the urinary tract produced inhibition of activity in both the jejunal and ileal loops (Tables I and II). For the most part, the

inhibition persisted only as long as the duration of the injection of the fluid; however, in some instances inhibition persisted for as long as five minutes after the fluid had been injected (Figs. 1 and 2). The animals experienced some discomfort while the upper part of the urinary tract was distended. Salivation occurred quite generally during the periods of distention and on one occasion (Dog 1) vomiting occurred.



Fig. 1.—The upper part of the left ureter was distended with 5 c.c. of saline solution injected through the ureteral catheter over a period of fifty-five seconds in the first instance depicted. Inhibition of motility of a jejunal loop developed immediately and was maintained for four minutes. In the second instance depicted, 5 c.c. of saline solution were injected over a period of fifty-five seconds; inhibition developed immediately and was maintained for six minutes. The time intervals represent five seconds and one minute.

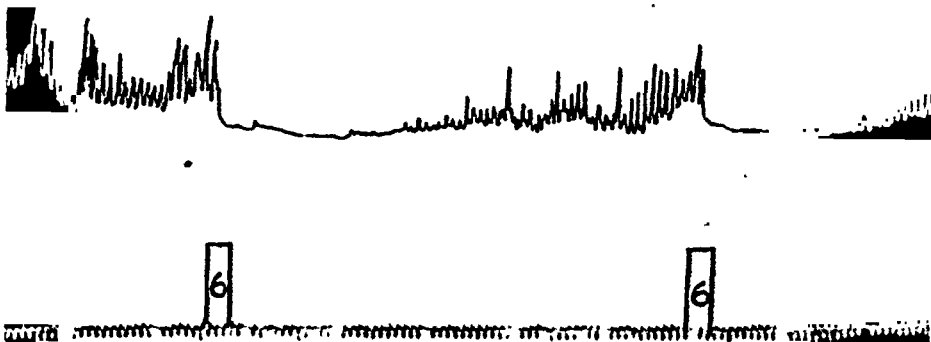


Fig. 2.—In the first instance depicted, 6 c.c. of saline solution were injected through the ureteral catheter into the upper part of the left ureter over a period of twenty seconds. Inhibition of motility of an ileal loop developed immediately and persisted for three minutes. In the second instance depicted, 6 c.c. of urine were injected over a period of twenty seconds; inhibition of motility developed immediately and persisted for two minutes. The time intervals represent five seconds and one minute.

*Distention of the Urinary Bladder.*—Studies were made on four dogs with exteriorized loops of the lower part of the ileum, ten to twelve inches (25 to 30 cm.) from the cecum, and on three dogs with exteriorized loops of the upper part of the jejunum, ten to twelve inches distal to the ligament of Treitz. The animals were fed 100 gm. of the semisolid dog chow before the experiment was started to insure intestinal activity.

*Regulation of Urinary Flow.*—Roughly equal amounts of urine were obtained on seven animals. Twelve to twenty c.c. were obtained on three animals. Urine in excess of twenty c.c. was obtained on one animal. The amount of urine obtained was regulated by the rate of flow of the urine from the bladder into the exteriorized loop of the jejunum or ileum. The rate of flow was regulated by the position of the exteriorized loop of the jejunum or ileum.

hibition began when as little as 20 to 50 c.c. of fluid were present in the bladder, while in other instances 200 to 250 c.c. were necessary to produce the effect. The amount of fluid in the bladder necessary to suppress motility varied from animal to animal and in the same animal from day to day. Usually, however, the effect could be elicited when less than 100 c.c. of fluid had been introduced rapidly into the bladder.

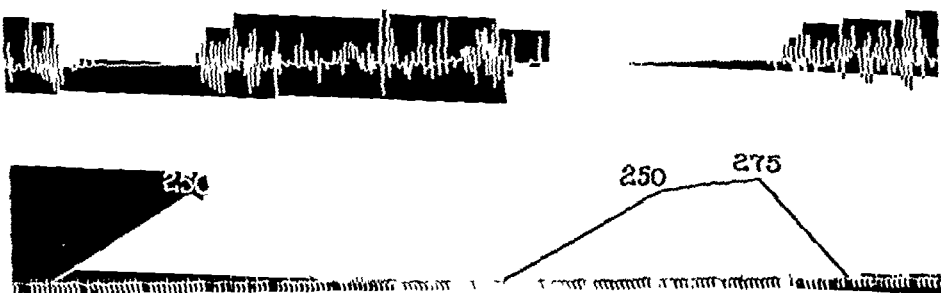


Fig. 3.—Loop of jejunum 10 to 12 inches (25 to 30 cm.) from ligament of Treitz. Bladder filled at rate of 100 c.c. in fifty seconds. Inhibition of intestinal activity occurred when 30 c.c. had been introduced into the bladder. Intestinal activity was resumed immediately after the catheter was opened. Time intervals represent five seconds and one minute.

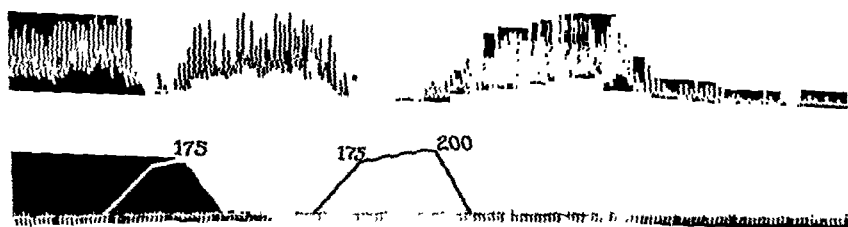


Fig. 4.—Bladder filled at rate of 100 c.c. in thirty-five seconds. Inhibition of activity of an ileal loop resulted when 100 c.c. had been introduced in the first instance depicted, and in the second instance, when 150 c.c. had been introduced. Resumption of intestinal activity occurred immediately after the catheter was opened. Time intervals represent five seconds and one minute.

Intestinal activity was resumed immediately after the catheter was opened and the fluid permitted to escape from the bladder.

*Slow Distention:* The urinary bladder is filled normally from the ureters at a rate of about 2 c.c. per minute. This rate of filling of the bladder was found to be too slow for animal experimentation, because the animal became fatigued and restless before the bladder could be overdistended at this rate. McLellan, in cystometric studies on human subjects, found that the optimal rate of filling of the bladder for determination of cystometric pressures was 5 c.c. per minute. After several preliminary determinations in which the element of fatigue of the animal was taken into consideration, it became apparent to us that the slowest rate of filling of the bladder suitable for animal experimentation by our method was of the magnitude of 7 to 14 c.c. per min-

TABLE III

SLOW DISTENTION OF THE URINARY BLADDER OF DOGS WITH EXTERIORIZED LOOP OF LOWER PART OF ILEUM

NUMBER AND WEIGHT OF DOG	RATE OF FLOW (C.C. PER MIN.)	CYSTOMETRIC PRESSURE AT ONSET OF INHIBITION (CM. OF WATER)	BLADDER VOLUME AT ONSET OF INHIBITION (C.C.)	FINAL BLADDER VOLUME (C.C.)	DURATION OF INHIBITION (MIN.)	CYSTOMETRIC PRESSURE WHEN INHIBITION OCCURRED (CM. OF WATER)
1 14 kg.	8	—	350	465	30	—
	8	—	340	430	18	—
	7	18	375	440	50	12-16
	7	27	380	435	62	16-50
	8	13	400	500	25	18-54
Average		19.3	369	454	37	15-50
2 13.5 kg.	7	18	360	375	29	16-18
	7	20	325	350	21	52-56
	7	17	360	160	14	14-60
	8	35	100	110	10	50-54
Average		22.5	361.2	398.7	26	18-54
3 12 kg.	7	27	330	355	38	50-56
	8	20	280	380	36	10-44
	14	22	280	280	10	50-54
	14	26	325	345	38	14-18
Average		23.8	303.8	340	30.5	16-50.5
4 8.5 kg.	7	30	210	250	29	10-18
	14	35	130	200	76	14-50
	14	33	70	100	16	54-60
	8	35	325	360	23	56-60
Average		33.2	183.8	227.5	36	18.5-54.5
Average of averages		24.7	304.4	355	32.3	16.9-52.2

ute. Therefore, in the experiments designated "slow distention" the bladder was filled at rates ranging between these limits.

Seventeen determinations were made on the four animals with ileal loops. Inhibition of intestinal activity occurred in every instance. However, a considerably larger volume of fluid in the bladder was necessary to initiate this reflex than when the bladder was distended rapidly. The range of volume of fluid in the bladder when inhibition occurred in these studies was 70 to 400 c.c., the average of the series being 304.4 c.c. It is to be borne in mind that these animals varied in size, and it is rational to suppose that the capacity of the bladder varies in direct proportion to the size of the animal. This assumption may serve, in part, to explain the wide range of volume of fluid in the bladder necessary to initiate the inhibitory reflex in the various animals. Thus, the animal in which 70 c.c. of fluid in the bladder produced inhibition of activity weighed 8.5 kg. (Table III), while the animal in which 400 c.c. of fluid in the bladder was necessary to produce the inhibition weighed 14 kg. When it is considered that the average weight of the adult dog is 25 kg., it is not surprising that the average volume of fluid in the bladder necessary to initiate inhibition of activity is 304.4 c.c. It is also to be noted that the average rate of flow of fluid into the bladder was 24.7 c.c. per minute, and that the average duration of inhibition was 32.3 minutes.



TABLE IV

SLOW DISTENTION OF THE URINARY BLADDER IN DOGS WITH EXTERIORIZED LOOP OF UPPER PART OF JEJUNUM

NUMBER AND WEIGHT OF DOG	RATE OF FLOW (C.C. PER MIN.)	CYSTOMETRIC PRESSURE AT ONSET OF INHIBITION (CM. OF WATER)	BLADDER VOLUME AT ONSET OF INHIBITION (C.C.)	FINAL BLADDER VOLUME (C.C.)	DURATION OF INHIBITION (MIN.)	CYSTOMETRIC PRESSURE WHEN URINATION OCCURRED (CM. OF WATER)
5 16 kg.	8	—	—	380	—	50-56
	12	—	—	550	—	48-54
	12	30	150	220	10	42-48
	12	—	—	430	—	46-50
	8	34	260	350	28	44-50
	8	—	—	400	—	48-52
Average		32	205	388.3	19	46-52
6 8.5 kg.	8	18	180	265	26	42-50
	8	22	200	275	23	44-48
	14	20	260	320	7	45-58
	14	20	50	100	16	56-60
	8	17	190	260	12	50-54
	14	18	220	275	13	46-52
Average		19	183	249.1	16.1	47-54
7 12.5 kg.	10	—	—	410	—	56-60
	11	—	—	390	—	48-52
	14	—	—	470	—	50-54
	7	19	410	450	16	42-46
	8	—	—	475	—	42-46
	10	—	—	500	—	46-52
Average		19	410	449.1	16	47-52
Average of averages		23	266.1	362	17.03	46.6-52.6

An interesting variation in response to slow distention of the bladder was noted in the animals with exteriorized loops of jejunum (Table IV). Three animals with such loops were studied in eighteen experiments. Whereas in the animals with loops of the lower part of the ileum inhibition was produced in every instance by slow distention of the bladder, in the animals with jejunal loops this phenomenon occurred in only nine of eighteen experiments, or in 50 per cent of the instances. This reflex was initiated on only one occasion in six attempts in one dog, twice in six attempts in another dog, and in all six instances in the third dog. The range of bladder volume when inhibition occurred was 50 to 410 c.c., the average volume being 266.6 c.c.

*Maintenance of Inhibition:* Once inhibition of activity of the small intestine was established by sustained distention of the urinary bladder, it persisted for a variable time, after which feeble, irregular peristaltic contractions began to occur. If at this point the volume of fluid in the bladder was enlarged by a relatively small increment, inhibition was re-established for a time, after which activity would again begin feebly. A state of quiescence could be re-established by again adding to the bladder volume by a small increment. This cycle of events could be repeated until the animal urinated or became so uncomfortable that the experiment was terminated.

Thus, in a study of Dog 1 (lower ileal loop) the bladder was filled at a rate of 7 c.c. per minute. Inhibition occurred when the bladder volume was 380 c.c. Quiescence of the small intestine persisted in a complete degree for twenty-nine minutes and in a relative degree for six minutes more. After this thirty-five-minute period of inhibition activity was resumed. Bladder volume then was increased by 30 c.c. (to 410) at the same rate of flow, and complete inhibition developed and persisted for five minutes, being followed by feeble, irregular con-

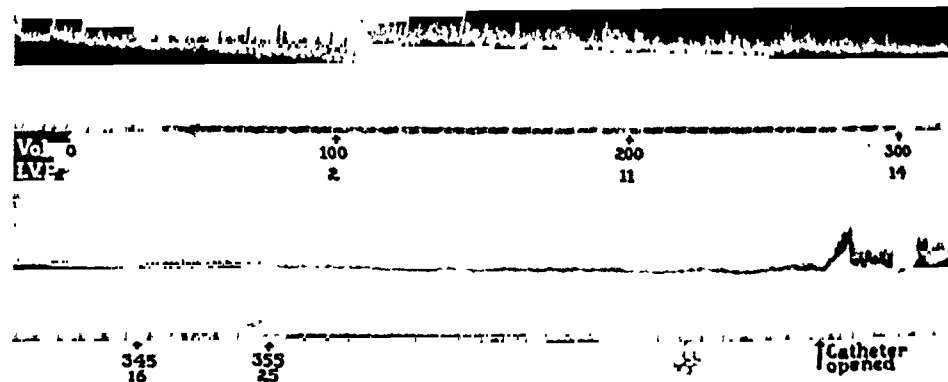
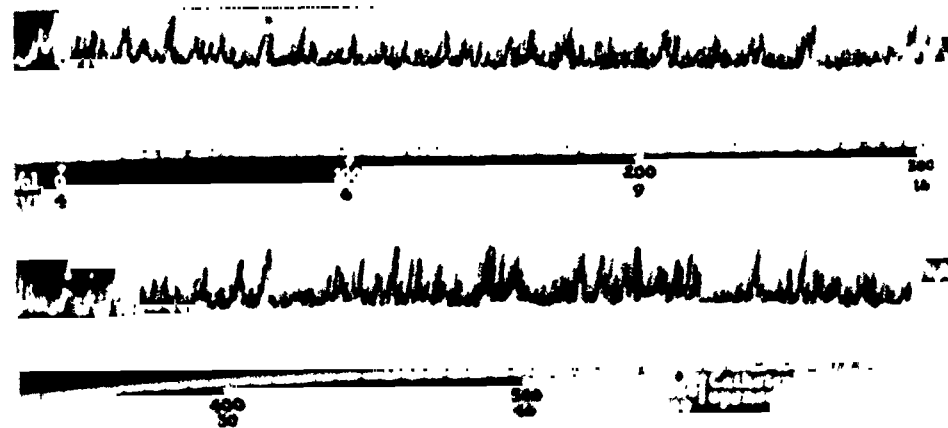


Fig. 5.—The bladder was distended at a rate of 7 c.c. per minute. When the volume of fluid in the bladder reached 330 c.c. inhibition of activity of an ileal loop occurred and persisted in a complete degree for six minutes and in a relative degree for six minutes longer. During this period of inhibition, the bladder volume had been increased at a uniform rate to 345 c.c. Activity then resumed and 10 c.c. were added to the bladder volume. This increment produced inhibition which persisted for twenty minutes in a complete degree and for six minutes longer in a relative degree. In all, then, inhibition was maintained in this instance for thirty-eight minutes. The experiment was terminated at this point because the animal experienced considerable discomfort. Time intervals represent five seconds and one minute. Vol.—volume in cubic centimeters, I.V.P.—intravaginal pressure in centimeters of water.



tractions (relative inhibition) for ten minutes longer. At this point activity again resumed. After 25 c.c. of fluid had been added at the same rate of flow, bringing the bladder volume up to 435 c.c. relative inhibition again began, persisting for a seven-minute period followed by a five-minute period of relative inhibition. At this point the animal urinated around the catheter. Thus, by adding small increments to the bladder volume from time to time, inhibition in this instance was maintained for sixty-two minutes. Another instance of the maintenance of inhibition of intestinal activity is illustrated in Fig. 5.

Seventeen experiments were performed on the four animals with lower ileal loops in an attempt to determine the length of time inhibition could be maintained by distending the bladder slowly. The average duration of inhibition obtained, as described previously, was 32.3 minutes, the range being ten to seventy-six minutes.

Here, again, a variance between the animals with jejunal loops and those with loops of the lower part of the ileum was noted. In three animals of the former group, slow distention of the bladder was per-

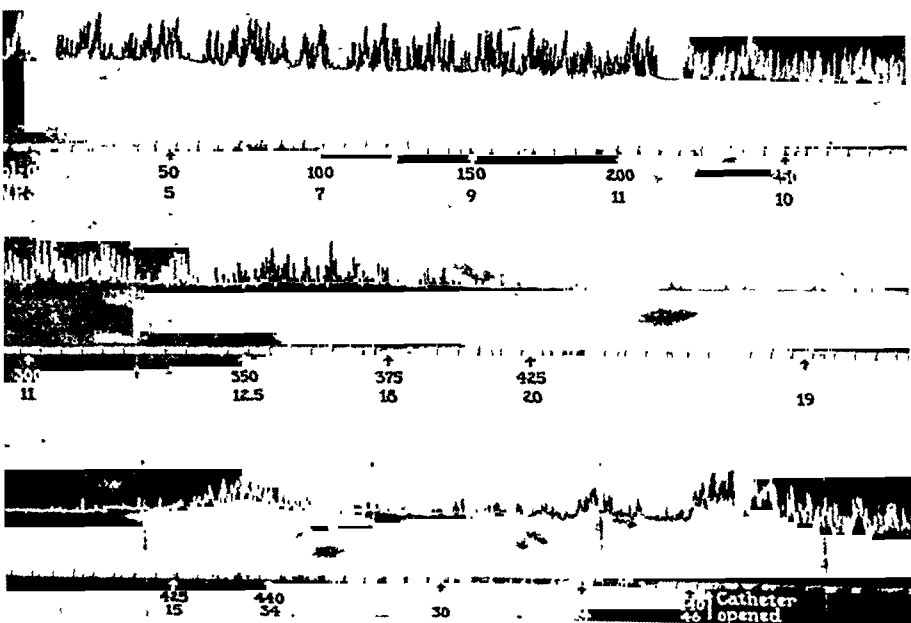


Fig. 7.—Fluid was introduced into the bladder at a rate of 7 c.c. per minute. The intravesical pressure gradually rose from 3 to 18 cm. of water, at which time inhibition of activity occurred with a volume of 375 c.c. in the bladder. After thirty-four minutes of inhibition (during the first seven minutes of which the bladder volume had been increased to 425 c.c.) the intravesical pressure had fallen to 15 cm. of water, at which time activity became re-established in the loop. The bladder volume then was increased by 15 c.c. (425 to 440 c.c.) in four minutes, after which intravesical pressure rose to 34 cm. of water, and a relative inhibition was re-established. The bowel remained relatively quiescent for sixteen minutes, during which time the intravesical pressure varied between 30 and 34 cm. of water. The animal was obviously uncomfortable at this point and was evidently attempting to urinate. As a result, the intravesical pressure rose sharply to 46 cm. of water, and the animal urinated around the catheter, after which intestinal activity immediately became vigorous and steady. Time intervals represent five seconds and one minute. Vol.—volume in cubic centimeters; I.V.P.—intravesical pressure in centimeters of water.

Thus, in a study of Dog 1 (lower ileal loop) the bladder was filled at a rate of 7 c.c. per minute. Inhibition occurred when the bladder volume was 380 c.c. Quiescence of the small intestine persisted in a complete degree for twenty-nine minutes and in a relative degree for six minutes more. After this thirty-five-minute period of inhibition activity was resumed. Bladder volume then was increased by 30 c.c. (to 410) at the same rate of flow, and complete inhibition developed and persisted for five minutes, being followed by feeble, irregular con-

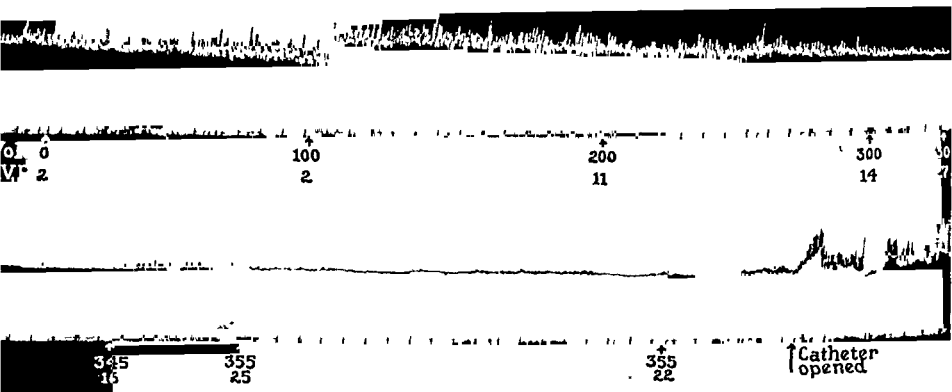


Fig. 5.—The bladder was distended at a rate of 7 c.c. per minute. When the volume of fluid in the bladder reached 330 c.c. inhibition of activity of an ileal loop occurred and persisted in a complete degree for six minutes and in a relative degree for six minutes longer. During this period of inhibition, the bladder volume had been increased at a uniform rate to 345 c.c. Activity then resumed and 10 c.c. were added to the bladder volume. This increment produced inhibition which persisted for twenty minutes in a complete degree and for six minutes longer in a relative degree. In all, then, inhibition was maintained in this instance for thirty-eight minutes. The experiment was terminated at this point because the animal experienced considerable discomfort. Time intervals represent five seconds and one minute. Vol.—volume in cubic centimeters; I.V.P.—intravesical pressure in centimeters of water.

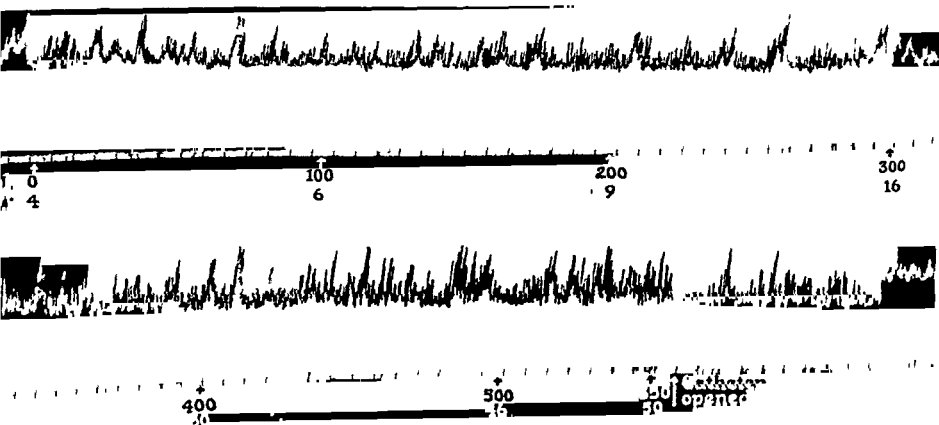


Fig. 6.—Loop of jejunum 10 to 12 inches (25 to 30 cm.) from the ligament of Treitz. No inhibition of activity resulted in this instance although the bladder was filled to 550 c.c. and the intravesical pressure rose to 50 cm. of water. Vol.—volume in cubic centimeters; I.V.P.—intravesical pressure in centimeters of water. Time intervals represent five seconds and one minute.

during the injection or immediately following the completion of the injection. The inability to withdraw fluid through the catheter would lead one to believe that the injected fluid produced only a very transient distention and then rapidly leaked down around the catheter into the bladder. Several attempts were made to block the ureter at the ureterovesical orifice by passing a ureteral catheter fitted with a suitably placed wax plug. However, owing to the inherent difficulties of passing a ureteral catheter in the dog, this method was discarded because the results were not often enough satisfactory to make it feasible.

From this study, we have shown that distention of the upper part of the urinary tract of dogs produces an inhibition of activity of the jejunum and the ileum which persists in most instances as long as the distention is maintained, and in some instances for variable periods up to five minutes after the distention of the upper part of the urinary tract has been released. These results are in accord with the findings of Campbell and Patterson, of Welch, Coplan, and Holmes, and of Coplan, who found similar inhibiting effects on gastric and colonic activity from distention of the upper part of the urinary tract. These studies offer a possible explanation for the reflex gastrointestinal symptoms noted clinically in cases in which there are proved disturbances of the upper part of the urinary tract.

From our findings, and from the results of King, who found that sudden distention of the urinary bladder produced diminution of duodenal activity, certain generalizations may be drawn: (1) Sudden distention of the urinary bladder produces inhibition of activity in all segments of the small intestine. (2) When the bladder is distended slowly, certain variations of the response of the various segments of the small intestine are noted. King found that no change of duodenal activity occurred when the bladder was distended slowly, and in our experiments, inhibition of jejunal activity occurred in only 50 per cent of instances. These results in the upper reaches of the small intestine stand out in marked contrast to the consistent and prolonged inhibition resulting in the terminal portion of the ileum from slow distention of the urinary bladder.

Two logical conclusions may be deduced from the foregoing: (1) Sudden distention of the urinary bladder gives rise to a stronger inhibitory intestinal reflex than does slow distention. (2) Activity in the upper segments of the small intestine is less readily inhibited than is activity in the lower reaches of the small intestine by distention of the urinary bladder.

It has been the observation of many physiologists that the duodenum and jejunum are more active and more responsive to stimuli than are the lower reaches of the small intestine. Houckgeest, Flöel, Biederman, Lüderitz, and Bayliss and Starling all mentioned this observation in their writings. Hosoi and Alvarez, as stated by the latter,<sup>1</sup> by holding a short segment of bowel under the bath of a salt solution and against

formed eighteen times. In nine instances no inhibition resulted (Fig. 6). In the nine instances in which inhibition did result, the average duration was 17.03 minutes, the range being seven to twenty-eight minutes.

*Cystometric Studies:* From the foregoing studies, one may theorize as follows: When the bladder wall is stretched sufficiently by a volume of contained fluid, impulses apparently arise which reflexly inhibit motility in the small intestine, particularly in the lower part of the ileum. As the wall of the bladder slowly accommodates to the volume of contained fluid, the tension in the wall is lessened and the inhibiting impulses are no longer generated. Motility therefore resumes; when the bladder wall is again stretched, by the addition of more fluid, inhibitory impulses are again sent out. Cystometric studies of intravesical pressures lend credence to this assumption.

It was found that, at the beginning of an experiment, when the bladder was empty, the intravesical pressure was of the order of 0 to 6 or 8 cm. of water. Inhibition of intestinal activity occurred at an average intravesical pressure of 23 cm. of water, the range being 11 to 35 cm. When intestinal activity re-established itself, the intravesical pressure usually had diminished to a value of 16 to 18 cm. of water. Urination occurred when the intravesical pressure reached an average value of 49.5 cm., the range being 46.6 to 52.2 cm. of water (Fig. 7).

#### COMMENT

One might be led to anticipate, from the knowledge of the work of Brush and Patterson, and of Fishback and Ivy, in which rather noticeable effects on gastric motility resulted from distention of the gall bladder, that the motility of the small intestine might be altered by distention of the gall bladder. However, no change in the peristaltic pattern of the jejunum or ileum, either in the recently fed or the fasted animal, was produced in any instance, even though the pressure in the gall bladder was raised to values far in excess of those employed by Brush and Patterson. The facts that, when pressures in excess of 140 mm. of mercury were applied to the balloon within the gall bladder, salivation occurred in 38 per cent of our cases, and considerable discomfort resulted in all instances, lead us to believe that in these experiments the gall bladder was being distended effectively. We can only conclude, therefore, that by our method of investigation, distention of the gall bladder through a pressure range of from 20 to 400 mm. of mercury does not produce any change in the activity of either the upper jejunal segment or the lower ileal segment of the small intestine.

Distention of the upper part of the urinary tract produced by the method employed in these studies persists only as long as fluid is being injected through the catheter. One could determine this objectively by noting that no fluid could be aspirated from the catheter at any time

## INTESTINAL ACTIVITY AFTER OBSTRUCTION OF COMMON BILE DUCT

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MANY physiologic alterations occur in obstructive jaundice. Some of the more important physiologic disturbances incident to obstruction of the biliary outflow occur in the gastrointestinal tract and considerable data have accumulated dealing with various gastrointestinal mechanisms, such as gastric secretion, intestinal absorption, and so forth, in the state of obstructive jaundice. The motor mechanism of the gastrointestinal tract in the presence of jaundice has not been thoroughly studied. Berti and Bernucci made a roentgenologic study of the small intestine in dogs after ligation of the common bile duct and found a delay in the passage of the opaque meal through the intestine. Gutzeit and Kuhlbaum conducted a similar study on a group of patients who had obstructive jaundice and on dogs after ligation of the common bile duct. Most of their patients had an incomplete obstruction of the duct. In their patients they found a decrease of intestinal activity that appeared to be due to depression of tonus contraction. In the dogs that had occluded bile ducts, the opaque meal reached the large intestine one or two hours later than in the normal state.

The purpose of our investigation was to study intestinal activity before and after ligation of the common bile duct using methods which permitted observation and recording of activity of loops of intestine under as nearly normal conditions as we have been able to devise.

### EXPERIMENTAL PROCEDURES

This study was made on trained dogs that had exteriorized loops of jejunum and ileum. The exteriorized loops of intestines were in continuity, with intact mesenteric blood and nerve supply and enclosed in bipedicle tubes of skin. All operative procedures were made with the animal under ether anesthesia and with aseptic technique. The recording of intestinal activity was done by use of an air-displacement system which consisted of a rubber balloon attached around the loop by means of a rubber cuff and in communication through a rubber tube with a recording tambour.<sup>3, 4</sup>

All the animals were trained to lie quietly throughout the period of observation. Each period of observation was preceded by an eighteen-to twenty-four-hour fast and continued for various lengths of time after feeding on the table. A standard meal, consisting of milk, syrup, and

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an electrode, were able to show a graded response from duodenum caudalward to electrical stimulation. Alvarez also noted a remarkable gradient in the tendency of excised segments of rabbit's intestines to resume rhythmic activity after the segments had been thrown into spasm with pilocarpine and then relaxed again with atropine. Alvarez has also shown that there is a gradient from a short latent period in the lower part of the duodenum to a long one in the ileum, a gradient of tonus, a gradient of irritability, and a gradient of rhythmicity from the duodenum caudalward. Puestow later confirmed Alvarez' gradient hypothesis of rhythmicity in the dog.

Our results are consistent with the hypothesis of a gradient of irritability from duodenum caudalward. Since the upper segments of the small intestine are more irritable than are lower segments, it would seem that the duodenum and the upper part of the jejunum are less readily inhibited and less readily kept under inhibition by a given stimulus than is the lower part of the ileum.

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A marked decrease of activity occurred during the first twenty-four hours after operation, followed by quick recovery which reached a maximum on the fifth to sixth day of biliary obstruction (Fig. 1). Subsequently, intestinal activity progressively decreased and usually minimal activity was reached during the twelfth to fifteenth days after occlusion of the duct. The decrease of activity was more noticeable in the loops of jejunum than in the loops of ileum. The feeding reaction gradually diminished and sometimes did not occur (Figs. 2 and 3).

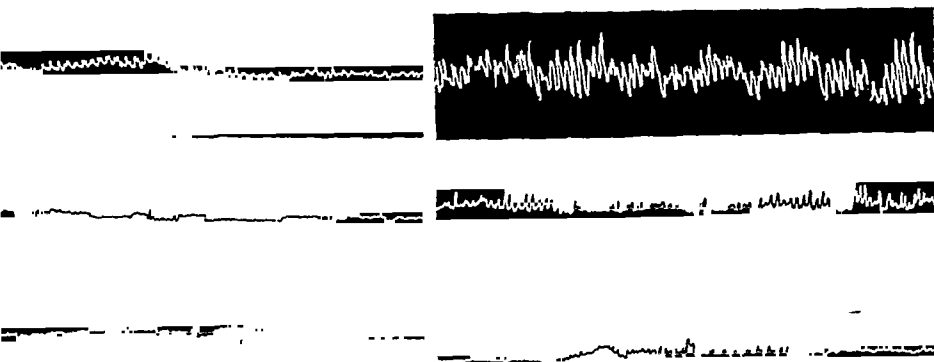


Fig. 3.—Intestinal activity of ileal loop, 15 cm. above the ileocecal valve. A, Control in fasting (left) and feeding (right) periods; B, six days after the obstruction of the common bile duct; C, fifteen days after the operation.

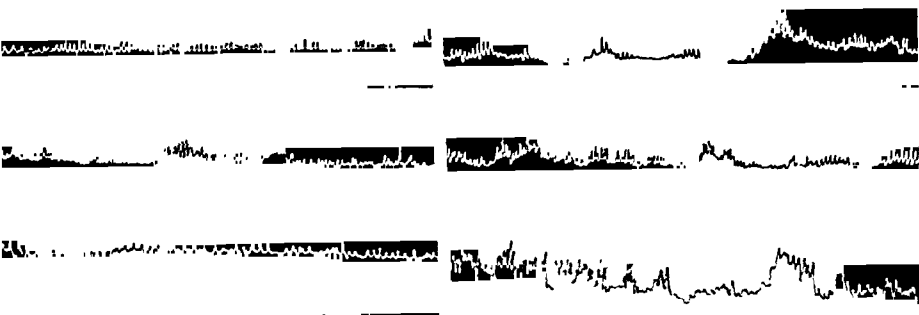


Fig. 4.—Same dog as in Fig. 2. A, In fasting (left) and feeding (right) periods, eighteen days after the obstruction of common bile duct; B, twenty-two days after the operation; C, thirty-eight days after the operation.

The periods of quiescence in the fasting period were often markedly prolonged. A definite increase of activity began between the fifteenth and twentieth days after operation, which was progressive throughout the remaining period during which observations were made, but never reached the amount that had occurred before ligation of the duct (Figs. 4 and 5). No changes of the frequency of the contractions were observed either before or after the obstruction of the duct.

bread, was given. This standard meal was used because it usually produces a characteristic motor response in the intestine of a fasted animal and the ingredients of the meal have been found most suitable for maintaining animals that have obstruction of the biliary outflow.

After sufficient control observations had been made, the animal was etherized and the biliary tract exposed. The gall bladder was removed and the common bile duct doubly ligated and sectioned. Observations were made repeatedly after obstruction of the biliary outflow during the period that the animals could be maintained in good condition, which varied from twenty-eight to thirty-eight days. Serum bilirubin was determined at various periods, using the van den Bergh technique.

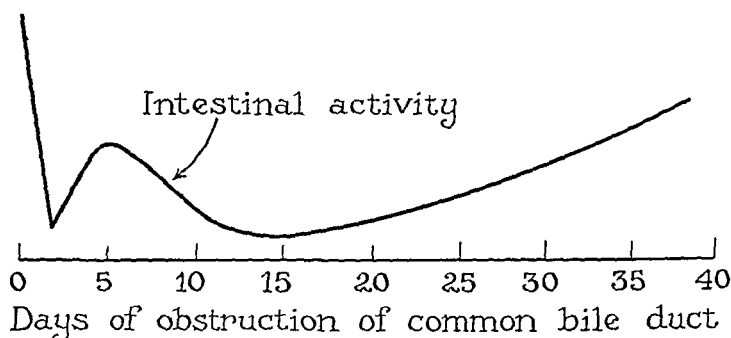


Fig. 1.—Diagrammatic representation of intestinal activity after ligation of common bile duct; curve made from kymograph records taken daily.

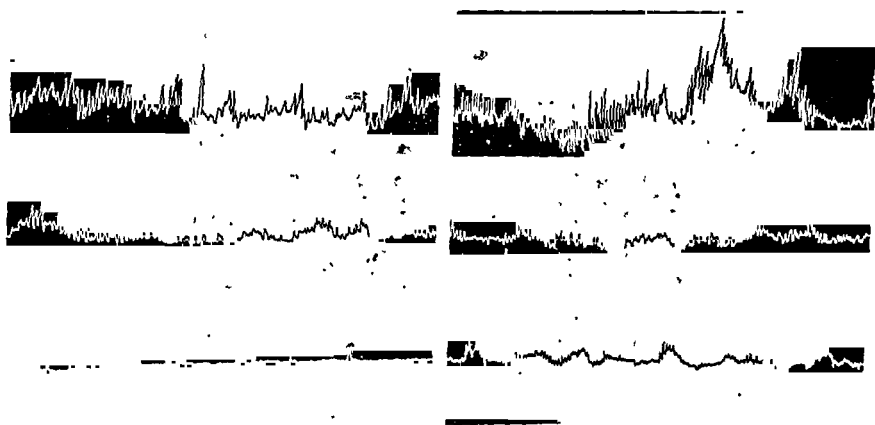


Fig. 2.—Intestinal activity of jejunal loop, 35 cm. from the ligament of Treitz. A, Control in fasting (left) and feeding (right) periods; B, five days after the obstruction of common bile duct; C, twelve days after the operation.

## RESULTS

In general, the effect of obstruction of the biliary outflow on the motor response of the intestine was similar in all the animals, and the changes that occurred affected all the types of intestinal activity, such as regular and irregular segmentation, tonus waves, and peristalsis.

The changes of intestinal activity that were noted in the animals that had obstructive jaundice might be owing to the lack of bile in the intestinal tract, accumulation of the biliary constituents in the blood, or both. Gutzeit and Kuhlbaum expressed the belief, from the results of their study on obstruction of the common bile duct, that lack of bile in the intestine is the primary factor for the decrease of intestinal activity. Horrall and his co-workers, using fasted dogs that had both duodenal and gall bladder fistulas, and several balloons inserted into the gut, concluded that the flow of bile into the intestine is an important factor in maintaining intestinal activity. Haney, Roley, and Cole came to the same conclusion as a result of their study on the local action of bile in Thiry-Vella loops. On the other hand, Ackerman, Curl, and Crandall, working with dogs in which bile was excluded from the intestine by anastomosis of the gall bladder to the right renal pelvis and ligation of the common bile duct, observed by means of the opaque meal that the motility of the intestine was not affected by the lack of bile. In one of the animals in our series, a spontaneous external biliary fistula developed nine days after occlusion of the common bile duct. Intestinal activity increased to a considerable extent after the restoration of the flow of bile even though the bile was excluded from the gut.

There is some evidence that the retained biliary constituents, particularly the bile salts, in the blood may be responsible for the decreased intestinal activity in obstructive jaundice. Schroeder, using guinea pigs, and Chabrol, Lemaire, and Cottet, using dogs, observed that the intravenous injection of bile or bile salts produced a great decrease and sometimes cessation of intestinal activity. Berti and Bernucci mentioned that small doses of bile given intravenously to dogs produced a marked delay of passage of the opaque meal through the intestine while large doses caused an acceleration of the intestinal transit. We injected gall bladder bile of the dog (0.5 c.c. per kilogram) and pure bilirubin (30 mg. per kilogram) intravenously into normal dogs and noted a definite decrease of intestinal activity. While the effect of bile salts when administered intravenously in a single dose may not be the same as when they accumulate gradually in the blood stream after obstruction to the biliary outflow, the depressing action of these substances on intestinal activity is suggestive. The fact, previously mentioned, that the changes of intestinal activity after obstruction of the common bile duct appear to have a relation with the changes of amount of bilirubin retained in the blood also suggests that the retained biliary constituents of the blood may be of importance in causing the alteration of the motor mechanism of the intestine that we observed. In this connection it should be noted that Snell, Greene, and Rowntree found that the fluctuations of the amount of bile salts in obstructive jaundice were similar to the changes in bilirubinemia.

The bilirubinemia increased gradually, reaching a maximum on the eighth or tenth day after operation. It subsequently progressively decreased to the end of the period of observation. There appeared to be an inverse relation between the changes of intestinal activity and the amount of bilirubinemia (Fig. 6).

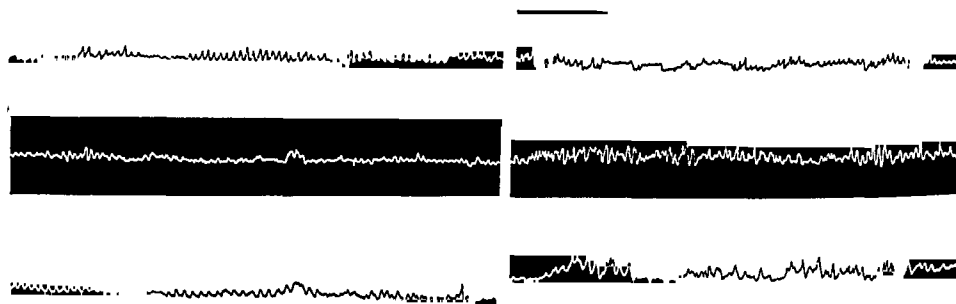


Fig. 5.—Same dog as in Fig. 3. *A*, In fasting (left) and feeding (right) periods, twenty days after the obstruction of the common bile duct; *B*, twenty-four days after the operation; *C*, thirty-five days after the operation.

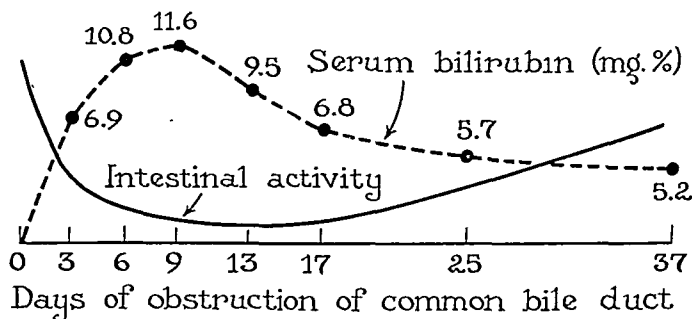


Fig. 6 (Dog 6).—Diagrammatic representation of the curves of bilirubinemia and intestinal activity after obstruction of common bile duct.

#### COMMENT

The sudden decrease of intestinal activity noted immediately after operation was apparently an effect of the anesthetic and operative procedures, and is in accord with previous observations. Golden found that intestinal activity is decreased greatly or abolished during surgical anesthesia but recovery often occurs with surprising rapidity. Mann and Wakim noted that an almost complete cessation of intestinal activity occurred for a few hours after ether anesthesia and exploratory operation involving exposure of the entire gastrointestinal tract for fifteen to twenty minutes. In each of the foregoing investigations, normal movements of the intestine were resumed within twenty-four hours after anesthesia. The changes of intestinal activity that were noted in this investigation after the animals had recovered from the immediate effects of the operation would appear to be the result of obstruction to the biliary outflow.

# THE EFFECT OF INTRAPERITONEAL INJECTION OF GASTRIC, STRANGULATED INTESTINAL AND APPENDICAL LOOP CONTENT UPON THE LEUCOCYTE COUNT

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IF ANY one of a number of protein substances, of which peptone is an example, be injected intravenously into animals, there occurs within a few minutes a striking reduction in the number of leucocytes in the circulating blood, and this reduction in leucocytes is due mainly to the disappearance of the granular forms. After a period of several hours, the leucocytes increase and often reach a level much higher than normal.

Wysocowitsch,<sup>19</sup> in 1886, was apparently the first one to note this phenomenon, and from that time until the present there have been many explanations as to the cause of the leucopenia.

Löwit,<sup>10</sup> in 1892, believed that there was an actual destruction of the cells because he found some degenerated white blood cells in the circulating blood, and he believed that various organs were able to break up the leucocytes. He injected peptone, nucleins, or sodium urate, and found the results to be the same. The leucocytosis which followed he considered to be a response from the bone marrow.

Goldscheider and Jacob<sup>4</sup> produced leucopenia by the injection of extracts of spleen, thymus, or bone marrow, and were of the opinion that the leucopenia was due to the collection of the white blood cells in the capillaries of the lungs, liver, and spleen as a result of a negative chemotactic influence on the leucocytes exerted by the injected substances. Schultz,<sup>14</sup> Gräff,<sup>5</sup> and Wells<sup>18</sup> held similar views.

Silverman<sup>15</sup> and Schilling<sup>13</sup> believed that the leucocytes collected in the capillaries as a result of mechanical obstruction of the capillaries, caused by swelling of the endothelial cells, and that the leucocytes were thus strained out of the circulation and kept in the organs.

Bruce<sup>1</sup> made sections of lungs, spleen, and liver during the period of leucopenia and found that there was a great increase in the number of leucocytes present in these organs.

Ewing<sup>7</sup> found that the normal liver contained 17,400 leucocytes per cubic millimeter, but during leucopenia the number rose to 40,000 leucocytes per cubic millimeter.

Doan and his co-workers<sup>2</sup> injected 1 Gm. of sodium nucleinate into rabbits and produced an immediate leucopenia which lasted several

## SUMMARY

Obstruction of the common bile duct was followed by a marked decrease of activity in exteriorized loops of jejunum and ileum during the first two weeks after operation. Subsequently, intestinal activity increased but never equaled the normal amount in the jaundiced animals. The decrease of intestinal activity occurred in both the fasting and digesting states but was more noticeable in the latter. It is suggested that the biliary constituents retained in the blood, particularly the bile salts, may be of importance in causing the observed alteration of intestinal activity.

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1912, stated that after perforation of the intestine in typhoid fever, the leucocyte count might rise, remain stationary, or suddenly fall. Livingston and Squires<sup>9</sup> studied fifty-five cases of typhoid fever in 1925 and found that there was a decided fall in the leucocyte count in 18 per cent after perforation but they did not specify whether more than one count was made after the perforation occurred. Harris and Feldheym<sup>6</sup> recently reported leucopenia in patients following the release of an obstructed loop of an intestine. The reduction was usually noted on the first to fourth postoperative days and often was very pronounced. In one patient, for instance, the count was 14,400 before operation and 1,950 on the third postoperative day. In another case, the preoperative count was 11,750 and on the first, second, third, and fourth postoperative days it was less than 3,000. They attributed the leucopenia to a toxin which was released from the obstructed bowel and which produced a temporary bone marrow paresis, and in their opinion the leucopenia was not related to sepsis and did not mean a bad prognosis.

Moon<sup>11</sup> introduced ground muscle pulp, brain, liver, or kidney into the peritoneal cavity of dogs and observed a progressive circulatory deficiency which had all the characteristics of shock. He found that hemoconcentration was present but did not report leucocyte counts.

#### EXPERIMENTAL PROCEDURES AND RESULTS

##### *Group I*

##### *Intraperitoneal Injection of Intestinal Contents*

In order to obtain the material injected into the peritoneal cavity of the four dogs studied in this group, strangulation of the bowel was produced in other animals as follows: Ether was administered by intratracheal intubation after induction in an ether box. No preliminary medication was given. Intestinal strangulation was produced by ligation of intestine, mesentery, and vessels with one-half-inch twilled cotton tape under aseptic conditions. The incision was closed in three layers (peritoneum and muscle, subcutaneous tissue, skin) with No. 8 cotton thread. The loop was removed sixteen hours after strangulation to forestall rupture and loss of the contents. These contents, usually 100 c.c. of bloody, foul-smelling fluid, were removed from an intact strangulated gangrenous loop of jejunum about two feet in length.

After the injection of intestinal contents all four dogs had a more or less lowered leucocyte count within fifteen minutes. Immediately upon injection the dogs became very ill, trembled, whined, and vomited. When released one hour after injection they were weak, nauseated, and dejected and all but one died in about eight hours. Five dogs were then injected with a coarsely filtered saline suspension of contents of normal bowel. In each case the content of the whole small intestine, which was milked out immediately after the death of an animal killed with ether, was mixed with saline solution and filtered through gauze.

hours and which was then followed by a marked leucocytosis which persisted up to four days. Leucopenia was found in blood taken from the right heart, from the peripheral vessels, and the lungs. They found an accumulation of neutrophile polymorphonuclear leucocytes in the parenchyma of the spleen. If the spleen were removed no leucopenia occurred, but leucocytosis set in immediately after the injection.

Wells<sup>17</sup> injected dead bacteria into rabbits and found a greatly increased number of leucocytes in the spleen and liver. He examined blood from the lungs and the bone marrow during the leucopenia and found a normal number of leucocytes present. He believed that the leucopenia was not due to negative chemotaxis or to mechanical obstruction to the passage of the leucocytes through the organs, but that it was a manifestation of a positive chemotaxis toward the bacteria which collected in the liver and spleen.

Webb<sup>18</sup> studied the leucopenia which occurs in horse serum anaphylaxis in dogs. He found no aggregation of leucocytes in blood from the liver, intestines, kidney, spleen, bone marrow, portal vein, or peripheral vessels. Blood from the pulmonary vein, however, he found to contain fewer leucocytes than blood from the pulmonary artery and sections from the lung showed collections of leucocytes in the capillaries.

Hill<sup>7</sup> made leucocyte counts on blood from the liver, from a peripheral vein, from the spleen, and from a mesenteric vein in dogs during peptone leucopenia and found that there was a leucopenia present in all samples. He could find no evidence of accumulation of leucocytes in the liver or the spleen.

Hill and Stoner,<sup>8</sup> while investigating the toxicity of the contents of strangulated bowel, found that a profound leucopenia followed within five minutes after the intravenous injection of such material into dogs. They found that the leucopenia preceded the clinical symptoms of such injections by as much as thirty minutes, while in some instances, leucopenia was present with no clinical symptoms. Leucopenia also followed injection of the content of normal bowel, of bowel content in simple obstruction, and of the transudate collected from obstructed and strangulated intestine. Stoner and Hill believe that this leucopenia is a manifestation of some type of shock, and that the symptoms produced (hyperpnea, prostration, tremor, vomiting) by injection of intestinal contents are probably signs of the same phenomenon. Although they did not make detailed studies of the differential count in these experiments, it seemed that the leucopenia was not as definitely due to a disappearance of the granular forms as is the case in peptone leucopenia.

Instances in which splenic, liver or other tissue substances, peptones, nucleins or intestinal contents are suddenly introduced into the blood by natural process are rare, but the invasion of some of these into the peritoneal cavity does commonly occur and the possibility that leucopenias similar to those produced by intravenous injections might result from intraperitoneal injections has not been investigated. Osler,<sup>12</sup> in



*Comment and Conclusions From Table I.*—When the contents of strangulated bowel are injected intraperitoneally into another animal there is a marked systemic reaction which usually results in death. About thirty minutes after the injection there is a pronounced drop in the leucocyte count in the peripheral blood.

When the contents of normal intestine are injected in the same manner, the systemic reaction is less severe and the animal usually recovers. The fall in leucocytes is not constant or pronounced but usually occurs.

## Group II

### *Intraperitoneal Injection of Gastric Contents*

In order to determine if leucopenia might occur following rupture of a viscus, we procured gastric contents by lavage of a dog's stomach one-half hour after eating white bread (Dogs No. 605 and 594) and by washing a stomach (removed from dog under ether anesthetic for one hour) with saline solution (Dog No. 606).

White bread was used as a stimulating meal to avoid the side effects which would probably follow intraperitoneal injection of the meat extract test meal usually used. However, because white bread is such a poor secretagogue, it was decided that histamine diphosphate (2.08 mg. intramuseularly) should be used in the remainder of the experiments in Group II. Gastric contents were removed one-half hour after injection of histamine and injected into Dogs 715, 716, 717, 718, and 719 after treatment as indicated in "Remarks." Results of such injections can be seen in Table II. All dogs in this group lived with the exception noted in Table II.

*Comment and Conclusions From Table II.*—When gastric contents are injected intraperitoneally a drop in leucocyte count occurs in over one-half the animals. This drop is not constant in degree or time of occurrence. The systemic reactions in this group were not as severe as in Group I. All animals in this group lived.

## Group III

### *Rupture of the Appendix*

The appendices of five dogs were ligated in such a way that venous return was stopped. This operation was done aseptically with intratracheal ether anesthesia after induction in an ether box, and with no previous medication. A cutting suture was fixed to the appendix in the distal one-third. At six hours the appendix was swollen to three times its former size and was black and gangrenous. *At this time these dogs had a leucocytosis.* Rupture of the appendix (produced by pulling the cutting suture) resulted in a drop in white blood count in three out of five animals, and an increase in signs of illness.

*Comment and Conclusions From Table III.*—When a gangrenous appendix is made to rupture by the use of a cutting suture the leucocyte count often falls. It is only rarely that it goes higher than it was

This material was then injected intraperitoneally. These dogs did not appear as ill as the former group and when released appeared normal. The leucocyte drop following injection in this group (Table I, B) was usually as definite at fifteen minutes as in the former group (Table I, A), but a significantly greater proportion recovered.

TABLE I  
INTRAPERITONEAL INJECTION OF INTESTINAL CONTENTS

<i>A. Contents of Strangulated Loop</i>								
DOG NO.	W.B.C. NORMAL	AMT. INJECTED (C.C.)	W.B.C. 5 MIN.	W.B.C. 15 MIN.	W.B.C. 30 MIN.	W.B.C. 1 HR.	COMMENT	
581	12400	20	12700	11000	3600	7500	Recovered	
584	18100	100	18600	14950	10750		Died in 15 hours	
574	15150	50	14200	11650	7900	6500	Became very ill up- on injection	
576	16800	50	12800	9650	7800	5150	Died during night	
<i>B. Contents of Normal Dog's Intestine</i>								
DOG NO.	W.B.C. NORMAL	AMT. INJECTED (C.C.)	W.B.C. 5 MIN.	W.B.C. 15 MIN.	W.B.C. 30 MIN.	W.B.C. 1 HR.	W.B.C. 1½ HR.	W.B.C. 24 HR.
575	17100	15	15400	16000				Recovered
578	8700	20	7850	6800				Recovered
577	31500	20	26500	18500	14600			26050
597	7750	50	5350	6150	6650	3250	1300	Died
598	8650	50	6650	4550	2950	1600	1000	Died

TABLE II  
INTRAPERITONEAL INJECTION OF GASTRIC CONTENTS

DOGS NO.	605	606	594	715	716	718	717	719
W.B.C. NORMAL	8450	15000	13000	11050	10800	16300	11250	12450
<i>Gastric Contents Injected</i>								
15 min.	8150	13100	11150	10300	10300	14300	3150	10700
30 min.	6500	8600	11350	11900	11450	11800	3000	11300
60 min.	6000	12700	5700	8250	13950	12500	3100	10600
1½ hr.	6700	12700	3850	6850	11150	14700	3900	9450
2 hr.	6550	11650	5750	7800	10950	11950	2700	8400
2½ hr.		11400	2450	6800	11200	16500	4100	6400
3 hr.	7850		7400					4400
4 hr.			11700					7400
5 hr.			14750					7900
21 hr.			20150	21550	29200	45300	9400	19400
							Died in 49 hr.	

*Remarks*

Dog No. 605 } Given 20 c.c. unfiltered gastric contents removed from healthy dog  
 Dog No. 594 } after meal of white bread  
 Dog No. 606 } Given 20 c.c. filtered saline suspension of contents of stomach re-  
                   } moved from dog under ether anesthesia  
 Dog No. 715 } Given 50 c.c. of unfiltered gastric contents removed one-half hour  
                   } after histamine stimulation; stomach was here lavaged with 300 c.c.  
 Dog No. 716 } of distilled water before injection of histamine and removal of contents  
 Dog No. 718 } Given 25 c.c. of filtered gastric content; stomach was not lavaged  
                   } (otherwise same as Dogs No. 715 and 716)  
 Dog No. 717 } Given 50 c.c. of unfiltered contents from unlavaged stomach removed  
                   } one-half hour after histamine stimulation; this dog, a female Scottish,  
                   } in estrus, died 49 hours after the injection

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TABLE III

## WHITE BLOOD COUNT FOLLOWING RUPTURE OF APPENDIX

DOG NO.	601	602	604	607	608
NORMAL	9450	9100			13500
<i>Appendix freed from mesentery, ligated, and cutting suture affixed</i>					
6 hr.					
Postoperative	18700	15650	18400	19000	29900
<i>Cutting suture removed, appendix ruptured</i>					
5 min.	16350	16250			
15 min.	16100	14250			
30 min.		15150	21200	10550	29050
60 min.	14800	13350	18350	6950	26000
1½ hr.		8350	15950	1850	26050
2 hr.		6600	19400	900	18000
2½ hr.		7500	16400	1900	17500
3 hr.		4650	21400	1950	18300
3½ hr.		3950	18900	3250	17500
4 hr.		4000	17500	3650	16650
4½ hr.		1400		2200	
5 hr.		2050	20560	Died	19150
5½ hr.					24650
6 hr.			17150		23650
6½ hr.			21850		22400
Died at	22 hr.	20 hr.	16 hr.	5 hr.	24 hr.

before rupture. The drop in the leucocyte count is not constant in degree or time of occurrence but occasionally a marked leucopenia develops.

It might be expected that the blood picture following rupture of a gangrenous strangulated appendix would be similar to that produced by injection of contents of a strangulated jejunal loop. However, symptoms appeared more rapidly in the latter, the leucopenia appeared more quickly, and the length of life was much shorter.

Dogs in the first (Table I, A) and the last (Table III) of these experiments seemed prostrate. They shivered, vomited, and their extremities became cold. They were acutely ill.

## SUMMARY

In an attempt to simulate the conditions which exist after an acute abdominal catastrophe such as the rupture of a peptic ulcer, the rupture of an acutely inflamed appendix, or the rupture of a section of gangrenous bowel, the above series of experiments were performed. In addition to the severe systemic reaction produced on the animals by these procedures, there was a notable tendency for the leucocyte count in the peripheral blood to fall. It seems reasonable to assume that such a drop in the leucocyte count may occur under similar circumstances in man, and that it has not been previously detected except in isolated cases is probably due to the fact that blood studies were not made at the appropriate times. If such a fall in the leucocytes does occur in man it may explain some of the unexpectedly low leucocyte counts which are not infrequently found.

closure. The mechanism of pain production is twofold, either a rapid stretching of the intestinal musculature or resistance to the strong peristaltic contractions of that layer. In many instances, particularly in partial simple obstructions, this accumulation is gradual, and the inevitable stretching of the bowel wall is sufficiently slow so that pain is not appreciated by the patient except at the moments when peristaltic rushes in the gut reach the distended area. This pain, occurring with the arrival of peristaltic rushes at the distended bowel, is the cramp commonly associated with intestinal obstruction.

The frequency of rhythmic pendular contractions in the jejunal muscle has been shown by Alvarez and associates to be about twice that of muscle from the terminal ileum. There is some reason to believe that the frequency of periods of increased local muscular activity, corresponding to peristaltic rushes, also follows a gradient. In cases in which the level of intestinal obstruction is in doubt, the frequency of cramps may occasionally be of aid, the cases presenting intervals less than 3 to 4 minutes tending to have high obstructions and those of eight to ten minutes, low ones. The appreciation of pain between cramps is probably a function of the rapidity with which material is accumulating above the obstructed area.

*Borborygmus.*—Gas is normally present throughout the intestinal canal, but in the small intestine, where activity is great, it usually does not collect in pockets large enough for x-ray visualization (Wangenstein). With the onset of obstruction and stagnation above, gas in quantity collects above a small quantity of fluid. Each peristaltic rush forces a little more gas and fluid into this closed space, resulting at first in gurgles, audible with the stethoscope at the moment of the height of the cramp. As the volume enclosed within the bowel above the obstruction increases, the wall of this bowel is stretched increasingly more tightly, and the pitch of the audible sound coming with each cramp rises correspondingly until it becomes the familiar tinkle or borborygmus of established intestinal obstruction.

*Vomiting.*—Distention of the small bowel is accompanied by reverse peristalsis from time to time, and regurgitation into the stomach with vomiting occurs. In complete ileal obstructions of two to three days' duration, the vomitus begins to assume a fecal character; the fecal vomiting appears later in partial obstructions, if it appears at all.

*X-ray Signs.*—Although some of the distention is due to fluid in the gut, the greater part of it comes from swallowed air, as Wangenstein and Rea have shown in dogs. The presence of this gas within the bowel is not helpful in producing physical signs of obstruction, but because of it x-ray diagnosis is accurate in the majority of cases. Scout films of the abdomen reveal a ladderlike arrangement of gas-filled coils of the small intestine. In obstructions of several days' duration, the ratio of fluid to gas increases, and upright films of the abdomen show definite

# TREATMENT OF SMALL BOWEL OBSTRUCTION\*

## PROCEDURE USED AT THE UNIVERSITY OF MINNESOTA HOSPITALS

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**A**LTHOUGH improved techniques in the management of obstruction of the small intestine have cut the mortality to a quarter of that obtaining twenty years ago, this affliction still commands a mortality rate between 18 and 20 per cent in the leading surgical clinics (Table I).

Discussion of the improvement which has occurred generally requires some discussion of the factors involved in small bowel obstruction. Anatomically speaking, there are but two types of intestinal obstruction, the simple obstruction (that which bars only the passage of intestinal content), and the strangulating obstruction (that which prevents also the flow of blood to or from the involved segment). Obstructions of either type may be partial or complete, according to the degree of interference with flow or intestinal content.

### MECHANISMS OF OBSTRUCTION

The mechanisms of obstruction, in the order of frequency in which they are seen at this clinic, are as follows: (1) External hernia; (2) intussusception; (3) adhesive bands, frequently found in association with (4) adhesions of the bowel to other structures with the formation of kinks which render the obstruction ever more complete as the degree of distention increases; (5) foreign body or obturation obstruction, in the majority of cases due to large gallstones reaching the gut by cholecystenteric fistulae (Rigler, Borman, and Noble); (6) volvulus; (7) internal hernias; (8) mesenteric vascular occlusion, and (9) neoplasms. Hernias, adhesive bands, volvulus, and, of course, mesenteric vascular occlusion are prone to lead to gangrene of the involved bowel and fatal peritonitis if operative intervention is not prompt. Intussusception also leads frequently to gangrene of the intussusceptum, but the *ensheathing* intussusciens remains viable and delays or prevents infection of the peritoneal space.

It is the obstructions due to adhesions of the intestine to other structures in the abdomen which are successfully treated by conservative management alone.

### THE MANNER OF ONSET OF SYMPTOMS AND SIGNS

*Pain and Cramps.*—The onset of obstruction is followed within a short time by accumulation of fluid, food, and gas above the site of

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thus altering the histology, impairing the viability of the gut, and opening a new avenue of absorption, namely, transperitoneal migration. That products of bacterial action may be the noxious substances so absorbed is indicated by the report by Poth and Knotts that the placing of succinyl sulfathiazole in closed loops prolongs survival of the animal 500 per cent. Afferent nervous impulses have been considered lethal (Antonicic and Lawson) but this has not been corroborated as yet, although nausea and vomiting with secondary disturbances of chemical balance may be so produced (Burget and co-workers).

In the case of strangulating obstructions, death may be due to shock or to peritonitis.

#### SUMMARY OF ESSENTIAL POINTS IN DIAGNOSIS OF SMALL BOWEL OBSTRUCTION

The essentials of diagnosis of simple small bowel obstruction, therefore, are:

1. Crampy abdominal pain
2. Vomiting, fecal if late
3. More or less abdominal distention
4. Minimal abdominal tenderness, localized
5. Borborygmi with the peaks of the cramps, and
6. X-ray findings on flat plate of the abdomen

Strangulating obstruction presents:

1. Pain, usually crampy, often persisting between cramps (often in the back)
2. Vomiting, fecal if late
3. Distention
4. Tenderness, usually over a considerable area
5. Borborygmi, unless the case is late enough for paresis of the gut to have occurred
6. X-ray findings
7. Spasm and rebound tenderness, and
8. Shock (occasionally).

#### TREATMENT OF SMALL BOWEL OBSTRUCTION

The preceding discussion indicates that proper therapy should consist of (1) restoration of the patient's water and mineral balance and of his blood pressure to normal, (2) relief of distention (either by intubation of the small bowel or by removal of the obstructing mechanism), and (3) resection of such gangrenous bowel as may be present. At clinics such as the Massachusetts General Hospital, where two-thirds of the patients are admitted in the first forty-eight hours of the attack, the emphasis has been laid on early operation before the onset of distention (McKittrick).

*Intubation.*—At this hospital, on the other hand, enough of the patients have arrived later than forty-eight hours after the onset of symptoms to have drawn attention to alleviation of already present distention as the primary problem. Wangenstein and Paine developed the

fluid levels in the distended loops of bowel. Furthermore, the degree of absence of gas visible in the colon is a good index of the completeness of obstruction, provided gas has not been injected with enemas. Although a barium meal outlines the obstructed bowel very beautifully, the barium sulfate is apt to cake and increase the completeness of obstruction. It is therefore to be condemned.

*Shock.*—In the case of unrelieved strangulating obstructions, gangrene of the bowel wall occurs, and peritonitis develops. Inasmuch as venous compression is greater than arterial, large enough quantities of blood may be lost into the lumen of the bowel and into the peritoneal space to cause early death from shock (Wangensteen).

*Back Pain.*—In addition to the symptoms already outlined as characteristic of simple small bowel obstruction, patients with strangulating obstructions are apt to experience sudden onset of the attack with severe, frequently constant pain, often low in the back as well as in the abdomen. In our experience, the low back pain can be ascribed to tension on the mesentery resulting from passage of gut into herniae, around adhesive bands, etc.

*Peritoneal Irritation.*—The escape of bloody fluid or seepage from the gangrenous gut leads to marked tenderness in the abdomen, with muscle spasm and rebound tenderness. Elevation of temperature and leucocytic count follow in a few hours.

*Palpable Loops.*—In certain cases the degree of obstruction is slight enough so that compensatory hypertrophy of the intestinal muscle above is adequate to prevent decompensation. Between these extremes are many patients with partial obstruction complete enough to give the symptoms already mentioned, but in whom sufficient hypertrophy occurs to permit visualization of the outlines of loops on the abdominal wall and palpation of them with the examining hand. This degree of hypertrophy can develop in seven to ten days of chronic partial obstruction.

#### CAUSES OF DEATH IN INTESTINAL OBSTRUCTION

The cause of death in bowel obstruction has been extensively studied and is not settled. In high obstructions, sufficient water, acid, and chloride are lost to lead to death in short order from dehydration, hypochloremia, alkalosis, and uremia (Hartwell and Hoguet). With obstructions at progressively lower levels, these changes become less evident, and in terminal ileal obstruction they are almost inconsequential. In these cases the deaths are due to one of two causes, either (1) prolonged distention or (2) gangrene of the bowel wall, the presence or absence of gangrene depending upon whether a simple or a strangulating obstruction is present.

The mechanism by which distention proves lethal is hotly debated. Sperling showed that a sustained intraluminal pressure of 15 cm. of water is capable of injuring the bowel wall through vascular stasis,



In patients in whom a Miller-Abbott tube has been passed into the lower reaches of the small bowel, feeding by mouth of a liquid or low residue diet is often feasible, even if the obstruction fails to relent. Such procedure greatly facilitates the metabolic preparation of the patient for operation.

*Signs of Relenting of the Obstruction.*—The appearance of gas in the colon, as recognized by x-ray scout film, or the passage of gas by rectum, indicates that the obstructive mechanism has relented. It is customary here to allow the tube to remain in place an additional day or two and to check the tolerance of the patient to cessation of suction for one-half day before withdrawal of the tube.

*Oxygen.*—Fine and associates have demonstrated that respiration of high concentrations of oxygen aids in diminishing the gaseous distention in cases of intestinal obstruction. The method has proved of aid in some cases here, but suction is a much more direct approach to the problem of distention, and oxygen is used only occasionally as an additional measure in those cases in which suction alone has proved not quite adequate.

#### RESULTS

In the period from June 1, 1938, to April 1, 1942, 130 patients suffering from obstruction between the ligament of Treitz and the cecum were treated at the University of Minnesota Hospitals. The present detailed study is concerned with 110 of these patients, most of the remainder being patients in whom obstruction of the small intestine was

TABLE I  
MORTALITY RATES AS THE RESULT OF OBSTRUCTION OF THE SMALL INTESTINE

Lewis (Cook County)	21.7%
Schlicke (Mayo Clinic)	17.8%
McKittrick and Sarris (Mass. Gen. Hospital)	20.0%
Johnston (Wayne and Detroit Receiving)	9.5% (excludes strangulation obstruction)
Leigh (College of Physicians and Surgeons, New York)	13.2% (selected cases)
Wangensteen, 1939 (Univ. of Minn. Hospital)	17.9%

TABLE II

CASES EXCLUDED FROM THE PRESENT STUDY BECAUSE OBSTRUCTION WAS ONLY AN INCIDENT IN DEATH FROM OTHER CAUSE

CAUSE OF DEATH	NUMBER OF CASES
Carcinomatosis	7
Congenital anomalies in newborn infants	5
Abdominal abscesses perforating the bowel	2
Subphrenic abscess and sepsis from ruptured appendix	1
Severe sepsis from ruptured appendix*	1
Tuberculous peritonitis	1
Riding embolus at bifurcation of aorta followed terminally by mesenteric thrombosis	1
Total	18

\*This patient survived the obstruction, but was still seriously ill from other complications of appendicitis at the time of this report.

siphon suction apparatus now in general use in this country, and have shown that constant suction on an inlying duodenal tube will decompress cases of simple small bowel obstruction. More recently, Miller and Abbott have perfected a twelve-foot double lumen tube tipped with a balloon which can be inflated through one lumen to facilitate passage of the tube down the small intestine.

Johnston, Abbott, and others have outlined many maneuvers which can be used to pass the tip of the Miller-Abbott tube into the duodenum. Abbott has recently reported the use of a stylet of leader wire to stiffen the tube sufficiently to cause it to pass into the pylorus directly, the stomach being dilated with 500 to 600 c.c. of air. This procedure has worked nicely in five of the seven cases in which we have tried it.

*Metabolism.*—Hartwell and Hoguet, in 1912, called attention to the value of large amounts of normal salt solution in the treatment of high obstruction, and clinical applications were made by Haden and Orr, and others. With this impetus, efforts have been made to give an adequate caloric intake by the paraoral route, as outlined by Collier and Maddock. At this hospital, a caloric intake in excess of 1200 calories a day is accomplished by the administration of 20 per cent dextrose solution not faster than 150 c.c. per hour. A proper level of plasma electrolytes and blood urea nitrogen is usually quickly attained by giving sufficient salt and water to permit excretion of a liter of urine and 2 to 5 Gm. of salt daily. The available vitamins are given parenterally. In patients unable to take food by mouth over a considerable period, the use of amino acid preparations and small amounts of human plasma, such as 100 c.c. daily, have become routine in an effort to maintain a normal nitrogen balance. Larger quantities are necessarily given if the plasma protein level is found to be low.

*Operative Procedures.*—Most important, the patient is watched closely at four- to six-hour intervals for evidences of peritoneal irritation or failure of decompression. Scout films of the abdomen are made from time to time. If a tube cannot be passed into the small bowel in forty-eight hours, and the obstruction persists with continuing distention, catheter enterostomy without exploration is the usual procedure. If passage of the tube is not followed by satisfactory decompression for any reason, catheter enterostomy is also indicated. In patients in whom satisfactory decompression is not followed by relenting of the obstruction, exploration as an elective procedure is undertaken to restore intestinal continuity.

If signs of peritoneal irritation appear, exploratory laparotomy is in order, regardless of the degree of distention. In this type of patient, sufficient hemorrhage is likely to have occurred to precipitate shock, and blood or plasma in quantity should be at hand before undertaking surgical intervention.

*Conservative Treatment of Simple Obstructions.*—Table IV shows the cases treated only by conservative therapy in which no gangrenous bowel was present at any time. It is evident that this is a small-risk form of treatment if one can be reasonably assured that the obstruction is of a type which will relent. Some patients, ten in all, obtained relief and recovery with gastric suction alone. When the Wangenstein tube was used, success in intubation of the duodenum was achieved in thirteen out of twenty-nine attempts. Intubation was accomplished in a somewhat greater proportion of trials with the Miller-Abbott tube. The Miller-Abbott tube is now used routinely on all cases of obstruction of the small intestine treated at this clinic.

*Operative Treatment of Simple Obstructions.*—The second major group of patients consists of cases treated operatively who proved to have no gangrenous bowel present. Table V presents the data for this group.

TABLE V  
SIMPLE SMALL BOWEL OBSTRUCTION  
OPERATIVE THERAPY

Total cases	62
Total patients	57
Total deaths	8
Case mortality	12.9%
Patient mortality	14.0%

Among the operations performed, catheter enterostomy first draws attention, for it is the procedure adopted when conservative management fails. The procedure is done by an almost perfectly aseptic technique, placing the catheter in an emptied segment of gut after the Witzel

TABLE VI  
SIMPLE SMALL BOWEL OBSTRUCTION  
CATHETER ENTEROSTOMY\*

Indications	
Failure to pass Wagensteen tube	6
Failure to pass Miller-Abbott tube	4
Failure to pass either tube	3
Fear of strangulation	1
Failure of Wangenstein tube to decompress	1
Blind loop	2
Failure of a previous enterostomy	1
Function	
Good	15
Poor	2
Patient died too soon to estimate	1
Mortality	
From enterostomy itself	2†
From other causes after successful enterostomy	4
Total cases	18
Total patients	17

\*The total number of enterostomies performed is not indicated in this table, as some have been done prophylactically at the time of resection of gangrenous bowel, etc.

†One patient died of perforation of the bowel at operation. The other developed a high intestinal fistula and died of anasarca thirty-eight days after operation.

a minor incident in death from some other cause. These special causes of death are given in Table II.

Inasmuch as the surgical treatment of obstruction is under consideration, two patients who died in the hospital early in the study period without having been seen by a surgical consultant are also excluded. One of these had a gallstone obstruction, the other an intussusception.

The corrected figures are shown in Table III. These are limited to small bowel obstruction cases treated by the surgical service in the three years and ten months under consideration. The variance between the case mortalities indicates that a smaller percentage of repeated admissions has occurred for obstruction recurring after conservative therapy, the result of a somewhat more aggressive attitude in the general treatment of intestinal obstruction.

TABLE III  
SMALL BOWEL OBSTRUCTION  
(UNIVERSITY OF MINNESOTA HOSPITALS)

JUNE 1, 1938, TO APRIL 1, 1942	
Total cases	117
Total patients	110
Total deaths	17
Case mortality	14.2%
Patient mortality	15.5%
JUNE 1, 1931, TO JUNE 1, 1938	
Case mortality	14.7%
Patient mortality	17.9%

The cases have been broken down into groups for study. Inasmuch as the use of the term strangulation implies constriction of blood supply and not yet loss of viability, it is somewhat ambiguous from the point of view of prognosis. We, therefore, have divided the cases into those which proved to have gangrenous bowel present at the time of admission or later, and those which did not have gangrenous bowel present. A second division separates those treated entirely by conservative methods from those treated by any type of operative procedure.

TABLE IV  
SIMPLE SMALL BOWEL OBSTRUCTION  
CONSERVATIVE THERAPY

INTUBATIONS OF THE SMALL BOWEL*				
TYPE OF TUBE	INTUBATION NOT ATTEMPTED	SUCCESSFUL INTUBATION	FAILURE IN INTUBATION	FAILURE FOL- LOWED BY ENTEROSTOMY
Wangenstein	2	13	5	9
Miller-Abbott	0	11	3	7
Total cases			32	
Total patients			30	
Deaths			0	

\*The figures do not check because of two patients in whom failure occurred with the Wangenstein tube, and in whom success was achieved with the Miller-Abbott tube.

*Operative Treatment for Patients With Gangrenous Bowel or Bowel of Doubtful Viability.*—The final cases for presentation are those with gangrenous bowel or bowel of doubtful viability which were treated operatively. These are presented in Table IX.

TABLE IX  
SMALL BOWEL OBSTRUCTION AND GANGRENE OF BOWEL  
OPERATIVE TREATMENT\*

Recoveries	
Resection of gangrenous bowel and primary anastomosis	10
Exteriorization with delayed closure	2
Inversion of small gangrenous area during hernioplasty	1
Deaths	
Reduction of gangrenous intussusception	2
Excision or exteriorization of gangrenous bowel in presence of gross pus or peritonitis	3
Total cases	18
Total patients	18
Deaths	5
Mortality	27.8%

\*Among the cases recovering are included three infants with gangrenous intussusceptions, two of which were resected with primary anastomoses, and one of which was exteriorized, secondary closure being accomplished at a later date.

#### RESULTS IN THE RECENT PAST

In the past two years, it appears to us that the management of obstruction of the small intestine has improved materially at the University Hospitals, due to a series of influences. Improvements in the maintenance of metabolic balance by parenteral routes of administration seem to have played a part, and concentration of responsibility for the care of most of these patients in the hands of two persons (J. R. Paine and Dennis) has led to a more aggressive attitude with regard to surgical intervention. In the care of cases presenting gangrenous bowel, in particular, this policy has been fruitful, no death resulting in the last thirteen such cases. The use of the closed, aseptic anastomosis described by Dennis three years ago, and also of the local implantation of sulfonamides, recommended by Varco and collaborators, has played a role in this improvement, and results will be detailed elsewhere (Dennis, 1942).

If the forty-six-month period under study is broken roughly into two divisions, considering the past two years separately from the preceding twenty-two months, the data of Table X are obtained.

TABLE X  
MORTALITY RATES FOR THREE CONSECUTIVE PERIODS  
(AT THE UNIVERSITY OF MINNESOTA HOSPITALS)

	1931 TO 1938 (WANGENSTEEN ET AL.)	JUNE 1, 1938, TO APRIL 1, 1940	APRIL 1, 1940, TO APRIL 1, 1942
Number of cases	190	60	37
Number of patients	156	37	33
Number of deaths	28	11	6
Mortality:			
Case (%)	14.7	18	10.53
Patient (%)	17.9	19.3	11.32

TABLE VII  
SIMPLE SMALL BOWEL OBSTRUCTION

OPERATIVE PROCEDURES	CASES	DEATHS
Enterostomy alone	13	3 <sup>1</sup>
Hernioplasty	19	1 <sup>2</sup>
Intussusception, reduction of	11	0
Enterolysis	4	1 <sup>3</sup>
Enter oanastomosis at an interval after enterostomy	2	1 <sup>4</sup>
Resections	2	1 <sup>5</sup>
Freeing of bands	2	0
Removal of gallstone alone	3	0
Enterolysis and resection	1	0
Enterostomy plus		
Lysis	1	1 <sup>6</sup>
Removal of gallstone	1	0
Enter oanastomosis	1	0
Freeing of bands	2 <sup>7</sup>	0

<sup>1</sup>Pneumonia at 12 days, rupture of the gut at operation, fecal fistula at enterostomy site with death from anasarca thirty-eight days postoperatively.

<sup>2</sup>Atelectasis five days postoperatively.

<sup>3</sup>Hemorrhage five days postoperatively.

<sup>4</sup>Anastomosis broke down (open anastomosis).

<sup>5</sup>Adhesive peritonitis preoperatively. Bowel healed well, but new adhesions formed. Patient died of lung abscesses, peritonitis, continued obstruction, and sepsis. Previous enterostomy.

<sup>6</sup>Pneumonia nine days postoperatively.

<sup>7</sup>In one of these cases, the distended bowel was decompressed at operation by Dennis and Wangenstein by an aseptic procedure suggested by them; it is being reported elsewhere (Wangensteen, 1912).

TABLE VIII  
SMALL BOWEL OBSTRUCTION AND GANGRENE OF BOWEL  
CONSERVATIVE THERAPY

Survival	
Perforation of appendical abscess into bowel	
Deaths	
1. Postoperative strangulation around an appendicostomy performed for decompression in cancer of colon; obstruction not recognized	
2. Postoperative strangulation of gut around old adhesive band. (Operation, amputation for diabetic gangrene.) Obstruction not recognized	
3. Mesenteric venous thrombosis, admitted after six days	
4. Intussusception, admitted moribund	
Total cases	5
Deaths	1

pattern (Wangensteen). Such a catheter may be removed by simple withdrawal after it has served the purpose of decompression, and obstruction never occurs at the point of such a procedure. Table VI shows our experience with catheter enterostomy.

The various operative procedures performed on the patients with simple small bowel obstruction are indicated in Table VII.

*Conservative Treatment of Patients With Gangrenous Bowel.*—The third major group of cases with which we are concerned encompasses those treated conservatively in whom gangrenous bowel was present. The data are presented in Table VIII. The four deaths are not to be construed as arguments against conservative therapy, for in two the presence of obstruction was not recognized at all, and the other two patients were moribund on admission.

Success in dealing with cases with frank gangrene has encouraged us to be more aggressive in operating upon cases presenting only minimal evidences of peritoneal irritation. The excellent record of McKittrick and Sarris in operating upon early cases of small bowel obstruction as emergencies is also a strong factor favoring this procedure. We feel that it is only by an intelligent, combined use both of the improved methods of small intestinal intubation and of the newer surgical methods of coping with the problem that further reductions in mortality can be accomplished.

#### CONCLUSIONS

1. Despite improvement in the past two decades, small bowel obstruction still commands too high a mortality rate.
2. Treatment consists of:
  - a) proper water and salt administration
  - b) decompression of the distended gut by nasal tube, or by catheter enterostomy, if the tube is inadequate
  - c) parenteral administration of sugar, plasma, etc., to give a complete metabolic balance
  - d) resection of gangrenous bowel, if present, and
  - e) late operative restoration of continuity of the bowel if the obstruction fails to relent spontaneously
3. Results of treatment of 110 patients with small bowel obstruction during the period from June 1, 1938, to April 1, 1942, are presented.
4. Our treatment of this condition is apparently improving.

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The six deaths which have occurred in the past two years are worthy of note. Three patients died because of faulty surgery, such as accidental rupture of the bowel during an enterostomy, poor placement of the catheter, and leaving defects in the abdomen through which internal herniations subsequently occurred. Two died from failure to recognize the presence of strangulating obstructions as postoperative complications, one after ileosigmoidostomy with appendicostomy for multiple carcinomas of the colon, and the other after amputation for diabetic gangrene. One died of adhesive peritonitis, despite repeated decompressions, following decompression of an obstructed colon by colostomy.

In the last year of the study period, twenty-seven patients have been treated with loss of but two, a mortality rate of 7.4 per cent. In this period there were five resections for gangrenous bowel. One of the deaths was due to failure to recognize obstruction at all and the other to adhesive peritonitis.

#### RELATION OF AGE AND DURATION OF ILLNESS TO OUTCOME

McKittrick is inclined to stress the importance of early treatment, and had no deaths in forty-three cases operated upon within twenty-four hours of the onset of the disease. Forty-four per cent of our cases arrived at the hospital in the first twenty-four hours of the illness; in this group the mortality was 7.8 per cent. Seventeen per cent arrived in the second twenty-four hours and presented a mortality of 10 per cent. About 39 per cent arrived after forty-eight hours; in this group the mortality was 20 per cent. Early treatment, therefore, is of great importance whether the conservative or the operative approach is employed.

McKittrick found that advanced age is a great hazard to the patient with small bowel obstruction. Our experience over the period under study shows a mortality rate of 13.2 per cent for those under 60 years of age, a rate of 30 per cent for those from 60 to 70 years old, and a rate of only 7.1 per cent for those over 70 years old. These figures imply that our series is too small for conclusions.

#### COMMENT

It at first appears that less emphasis is being placed upon conservative therapy at this clinic than was the case at the time of the last report (Wangensteen, Rea, Smith, and Schwyzer). The reason for this is largely the success which has attended anastomosis in the presence of marked degrees of obstruction and gangrenous bowel, when performed by the closed technique. Inasmuch as the intestinal bacterial count can be reduced by oral administration of succinyl sulfathiazole preoperatively in operations of *election* (Poth), the closed anastomosis with local sulfathiazole implantation finds its field of greatest usefulness in *emergency* obstruction cases.



# PENETRATING GUNSHOT AND STAB WOUNDS OF THE ABDOMEN

## A REVIEW OF 336 CASES

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AN ANALYSIS of sixty-nine gunshot and stab wounds at the Louisville City Hospital was made by McKeithen<sup>1</sup> in 1927. The present series covers the past ten and one-half years. One of us (J. E. H.) has personally supervised this branch of traumatic surgery since late 1938. During the period from January, 1930, to July, 1941, 227 patients with gunshot and 184 with stab wounds of the abdomen have been admitted to the hospital. Thirty-seven gunshot and thirty-eight stab wound cases have been discarded, leaving for the present study, 190 perforating gunshot and 146 perforating stab wounds of the abdomen.

The discards were made for the following reasons: Sixteen bullet and thirty stab wounds were found nonpenetrating upon exploration of the abdomen. All the patients with negative explorations recovered uneventfully. Twelve patients with bullet wounds and five with knife wounds expired upon reaching the ward or within a few minutes thereafter. It seemed reasonable to discard as moribund these patients dying in less than an hour of admission, since they were doomed regardless of treatment. It is to be emphasized, however, that nine other cases (eight gunshot and one stab), although never coming to operation, were included in the present series. All but one of these patients were admitted in the earlier years and all were vainly "treated for shock" for from one to six or eight hours until they finally died. Although not operative deaths, these cases were nonetheless surgical casualties, for no operative measures were taken to control the bleeding that was undoubtedly responsible for their collapse and death.

A third group of discards consists of nine shotgun and three ice-pick wounds. We agree with Willis<sup>2</sup> that bird-shot wounds from a sufficient distance to show a definite shot pattern on the abdomen are best treated with conservatism unless continued bleeding is suspected. Surgical repair of the many tiny puncture wounds in the bowel which almost always seal themselves, has proved needless and futile. Shotgun wounds at close range are nearly uniformly fatal because of the terrible damage produced. Ice-pick punctures, uncomplicated by severe hemorrhage, are treated because of their smallness on the same expectant rationale as shotgun wounds. Therefore, since in most of these cases it could not be proved whether or not perforation occurred, the whole group was excluded. The three patients with ice-pick wounds recovered. Three

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operative mortality for the 182 gunshot cases and 145 stab wound cases that came to surgery is 48.9 per cent and 13.8 per cent respectively. These figures compare favorably with the average in the literature, which is about 57 per cent for bullet wounds and about 24 per cent for knife wounds. Fleming and McClamroch<sup>14</sup> report an operative mortality of 46.8 per cent for 111 perforating gunshot wounds of the abdomen. This is the lowest mortality we have found among larger series.

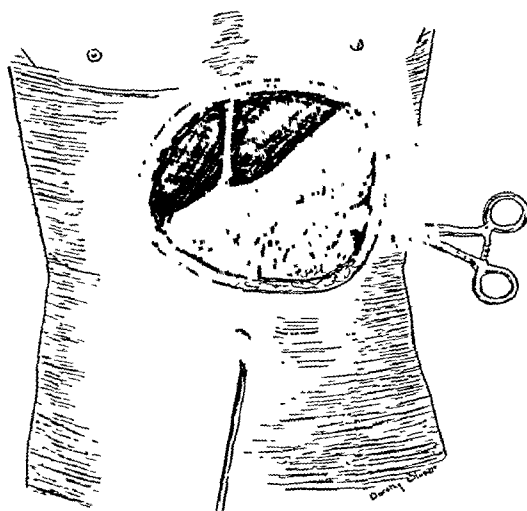


Fig. 1.—Illustrating how a hemostat, inserted through the suspected stab or gunshot wound, will indent and localize the underlying peritoneum for inspection through the peritoneoscope. (Courtesy Am. J. Surg. 54: 668, 1941.)

TABLE II  
CAUSE OF DEATH

CAUSE OF DEATH	GUN		KNIFE	
	NO. CASES	MORTALITY (%)	NO. CASES	MORTALITY (%)
Shock and hemorrhage*	35	56.7	6	28.6
Peritonitis†	25	25.8	7	33.3
Pulmonary	12	12.4	1	4.8
Other or not recorded	5	5.2	7	33.3

\*Fatal shock not associated with considerable hemorrhage occurred only three times, all gunshot.

†In a few of these cases pneumonia also was present.

*Cause of Death.*—It will be seen from Table II that by far the greatest single cause of death among the gunshot cases is shock and hemorrhage, with peritonitis less than half as frequent. As might be expected in stab injuries associated with relatively little bleeding, peritonitis from hollow viscus injury is the chief cause of death. Of the sixty-three cases of fatal shock (both gunshot and stab wound), all but three were accompanied by large hemorrhage. The preponderance of hemorrhage and shock in causing death is also pointed out by Fleming and McClamroch,<sup>14</sup> Loria,<sup>15</sup> Oberhelman and LeCount,<sup>17</sup> Taylor,<sup>13</sup> and Wilson.<sup>6</sup>

of the nine with shotgun injuries died. One of these, shot at close range, was moribund at entry. The other two, although showing a shot pattern, succumbed, apparently to hemorrhage and shock. These latter two probably should have been explored.

#### DIAGNOSIS

The presence of a gunshot or stab wound is obvious. The real difficulty that occasionally arises is whether or not the peritoneal cavity has been penetrated, for if it has, exploratory laparotomy is, with the exceptions already noted,<sup>3</sup> obligatory.<sup>4-7</sup>

TABLE I

INCIDENCE OF VOMITING AND OF SIGNIFICANT PAIN, SPASM, AND TENDERNESS

	VOMITING	PAIN	SPASM	TENDERNESS
Number of cases	19	24	27	30
<i>Nonpenetrating</i>	10%	62%	22%	33%
Number of cases	22	36	37	38
<i>Penetrating s injury</i>	9%	64%	22%	37%
Number of cases	72	129	171	150
<i>Penetrating c injury</i>	46%	82%	68%	74%

The unreliability of the history and physical findings in diagnosing penetration or visceral injury<sup>7, 8, 9</sup> is shown in Table I. It is surprising both that a greater percentage of the seriously wounded do not show significant symptoms and signs and also that these signs and symptoms are so frequently present in cases with no penetration of visceral trauma.

Penetration is obvious when protruding omentum is found. Evisceration of omentum (or rarely bowel) occurred fifty-two times among the stab wounds, an incidence of 36 per cent, and only twice in all the gunshot cases. The passage of blood by mouth, rectum, or urethra points to injury of the stomach, lower bowel, or urinary tract. However, it has been generally agreed heretofore that when the question of penetration cannot be otherwise answered, surgical exploration is indicated.<sup>6, 7, 10, 11</sup>

Since late 1938, we<sup>12</sup> have used peritoneoscopy in these doubtful cases to diagnose presence or absence of perforation (Fig. 1). We have employed this procedure, so far, fifteen times and without error. Eight times peritoneal perforation was ruled out and laparotomy avoided and in the other seven cases perforation of parietal peritoneum was disclosed and surgical exploration definitely indicated. It will be recalled that forty-six cases (13.7 per cent) were excluded from the present series because of nonpenetration, the same proportion as found by Taylor,<sup>11</sup> (13.8 per cent). Peritoneoscopy could have given the same information in practically every case and thus would have eliminated needless explorations.

#### MORTALITY ANALYSES

The total mortality for the 190 gunshot wounds is 51 per cent, for the 146 stab wounds, 14.1 per cent, combined, 32.1 per cent. The

less, the rate increased consistently with the increasing duration of operation. The high mortality of the briefest-operation group of gunshot wounds is largely attributable to hemorrhagic shock, which was responsible for death in 55 per cent of cases as against 48 per cent in the remaining time groups combined. Furthermore, 46 per cent of patients whose surgery lasted an hour or less, died on the table, while only 8 per cent of those with more prolonged operation did so.

The remarkably low mortality rate among stab wounds with operating time an hour or less is due to the fact that 69 per cent of them had no visceral injury.

TABLE VI

OPERATING TIME OF FATAL AND NONFATAL GUNSHOT CASES AND OPERATIVE MORTALITY IN SEVERAL SERIES\*

AUTHOR	NO. CASES	AVERAGE OPERATING TIME		OPERATIVE MORTALITY (%)
		LIVED (MIN.)	DIED (MIN.)	
Oberhelman and LeCount <sup>17</sup>	301	72	76	61.4
Taylor <sup>13</sup>	101	75	85	60.0
Prey and Foster <sup>21</sup>	22	55	70	68.0
Hamilton and Duncan	182	102	112	48.9

\*Unfortunately these are the only series with figures adapted to this comparison.

It has been urged by some<sup>21</sup> that great speed in operating is essential to save these patients. However, this is not borne out by Table VI. Rather, it seems that the rising mortality as the operating time increases is due, not to length of procedure per se, but to the increasing damage to be repaired. Furthermore, Rippey<sup>15, 22</sup> points to the increased incidence of missed visceral perforations in too-hurried operations. Unfortunately, only thirty autopsies were performed in this group, excluding cases of death on the table and nonoperated cases. Overlooked hollow visceral perforations were found nine times (30 per cent). This is below the average of the literature:

Oberhelman and LeCount <sup>17</sup>	55.6%	of	169	autopsies
McGowan <sup>19</sup>	55.5%	of	27	autopsies
Taylor <sup>13</sup>	43 %	of	14	autopsies
Billings and Walking <sup>16</sup>	19 %	of	49	autopsies
Rippey <sup>22</sup>	50 %	of	12	autopsies
Wilson <sup>6</sup>	50 %	of	20	autopsies

Some of these statistics, however, include injury to solid as well as to hollow viscera.

*Mortality Related to Viscera Injured.*—There is inevitably some overlapping in Table VII. Thus, if jejunum and colon were both perforated, a single entry of the more serious injury, namely of the colon, is made. Likewise, even though there may have been numerous bowel perforations in a given case, if death was obviously due to hemorrhage and shock, it is not recorded as bowel injury. If a solid and a hollow viscus were both injured and the patient died within the shock period (the first forty-eight hours) and obviously not from peritonitis or sepsis

TABLE III  
EFFECT OF AGE ON MORTALITY

AGE (YEARS)	GUN		KNIFE	
	NO. CASES	MORTALITY (%)	NO. CASES	MORTALITY (%)
0 to 20	31	45	18	0.5
21 to 40	130	47	101	11
41 to 60*	24	75	21	28.6

\*There were six patients over 60 years of age, one with fatal gunshot, two with fatal and three with nonfatal stab wounds.

*Effect of Age on Mortality.*—It is noteworthy (Table III) that for the gunshot cases where hemorrhage plays a far greater role than in stab wounds, the big interval in mortality comes after the age of 40. This is in agreement with Rippey's<sup>15</sup> series and suggests that one of the reasons for the greater vulnerability of the older gunshot patients is that their arteriosclerosis prevents effective vasoconstriction, nature's hemostat. Allen and Benedict<sup>20</sup> explain similarly the greater hazard of bleeding duodenal ulcer in patients 50 years of age or over.

TABLE IV  
EFFECT UPON MORTALITY OF TIME INTERVAL FROM INJURY TO OPERATION

TIME INTERVAL	GUN		KNIFE	
	NO. CASES	MORTALITY (%)	NO. CASES	MORTALITY (%)
2 hours or less	24	37.5	17	0
2 to 4 hours	87	51.7	62	11.2
Over 4 hours	34	50	31	16.1

*Interval Between Injury and Operation.*—Table IV reveals a consistent increase in stab-wound mortality as the time lengthens between injury and operation. This is to be expected since the chief cause of death in patients with stab wounds is peritonitis. The slight decline in mortality when gunshot wounds are over four hours old is undoubtedly due to the fact that hemorrhage, the largest cause of death, will have eliminated previously the worst-risk cases. The chief danger remaining for those with delayed operation will be peritonitis and pneumonia (See Table II again).

TABLE V  
EFFECT ON MORTALITY OF DURATION OF OPERATION

OPERATING TIME HOURS	GUN		KNIFE	
	NO. CASES	MORTALITY (%)	NO. CASES	MORTALITY (%)
1 or less	20	55	18	5
1 to 1½	19	39	51	14
1½ to 2	54	44	26	12
2 to 2½	36	53	14	9
Over 2½	23	70	9	44

*Duration of Operation.*—In the case of the bullet wounds (Table V), aside from the high mortality where operating time was one hour or

was also significant injury above the diaphragm (moderate to severe hemothorax, pneumothorax and/or pulmonary damage) is 60.8 per cent for gunshot and stab wounds together, as against 31.9 per cent where the injury was entirely abdominal. Wilson<sup>6</sup> also records similar findings: 76.3 per cent mortality, chest and abdomen; 47.0 per cent abdomen alone.

Of the twenty-one fatal cases with significant thoracic injury, this injury was probably the chief lethal factor eleven times. Therapeutic interference, such as thoracentesis, was recorded in only three of these eleven cases, although such interference might have materially improved the critical condition of seven of the remaining eight patients. Of the twenty-one fatal cases, thoracentesis with or without reinfusion of hemothorax blood was performed in only seven cases (33 per cent), whereas this procedure was carried out in eight of the thirteen surviving cases (62 per cent). In one of the surviving cases, 500 c.c. of blood were aspirated and returned to the patient. In one of the fatal cases, practically moribund at the time, 2000 c.c. of blood were removed in a single aspiration from the right pleural space and returned by autotransfusion. This greatly improved the patient's blood pressure and general condition. He grew gradually weaker in spite of repeated thoracenteses and transfusions of bank blood and died the third hospital day. Too late, it was realized that his decline had probably been produced by continued active bleeding from a lacerated liver and might have been corrected by timely laparotomy. Unfortunately, an autopsy was not obtained.

Too often, preoccupation with the abdominal injuries overshadows serious and often ameliorable damage above the diaphragm. Occasionally, an initial negative chest examination or x-ray film will lull suspicions, only to have the autopsy reveal massive hemothorax or pneumothorax, or both.

TABLE VIII  
EFFECT OF HEMORRHAGE ON MORTALITY

HEMORRHAGE	GUN		KNIFE	
	NO. CASES	MORTALITY (%)	NO. CASES	MORTALITY (%)
Small	79	27.8	107	9.3
Medium	39	51.3	14	14.3
Large	64	73.4	18	33.3

*Effect of Blood Loss on Mortality.*—Table VIII shows a striking and consistent increase in mortality with increasing hemorrhage. Blood loss reported in this paper is graded in the customary fashion:<sup>22</sup> Small, 500 c.c. or less; moderate, 500 c.c. to 1000 c.c.; large, 1000 c.c. or over. The tremendous influence of hemorrhage upon mortality in these perforating abdominal injuries is generally recognized (Billings and Walking,<sup>16</sup> Loria,<sup>24</sup> Mason,<sup>25</sup> Rippey,<sup>15</sup> and Taylor<sup>13</sup>).

TABLE VII  
MORTALITY OF VARIOUS VISCERAL INJURIES

VISCERA INJURED	NO. CASES	TOTAL MORTALITY (%)	MORTALITY BY BLOOD LOSS (%)	
			SMALL	LARGE
Stomach and duodenum	26	23.0	0	100.0
Jejunum	17	12.5	14.3	0
Ileum (including 5 unlocalized small bowel injuries)	24	25.0	7.1	55.5
Ileum and colon	13	23.0	10.0	66.6
Colon	40	40.0	47.0	50.0
Solid viscera	64	36.0	0	51.1
Great vessel	13	100.0	--	--
Abdomen and chest	34	60.8	--	--
Abdomen and urinary bladder	11	36.4	--	--
Abdomen and pancreas	7	71.3	--	--

death is attributed to the solid viscus injury alone. Conversely, if the death had been from peritonitis, it would be credited to the bowel injury.

The influence of large hemorrhage toward a lethal outcome in the various visceral injuries is striking. The only exception is presented by the jejunal perforations. The two fatalities in this group were associated with negligible blood loss.

Perforation of stomach and duodenum carries a rather high mortality because of the relatively large associated blood loss, the difficulty of exposure, and the frequency (73 per cent) of significant associated thoracic injuries.

There is, as we might expect, a progressive increase in mortality from peritonitis as the level of bowel perforation descends from jejunum to colon.

The apparently high mortality of associated urinary bladder perforation is deceiving, since in each of the four fatal cases the bladder injury was merely incidental in a general picture of hemorrhage and shock terminating on the operating table or within twenty-four hours.

The seven instances of pancreatic injury were associated with other more serious trauma. Four of the five fatal cases died within twenty-four hours, of obvious hemorrhagic shock. In the one autopsied case there was fat necrosis within the lesser sac, but apparently this did not contribute significantly to the fatality. The fifth patient died on the fourth day of lobar pneumonia. These findings do not corroborate the disastrous enzymatic digestion that Eisberg<sup>22</sup> holds will follow pancreatic injury.

The uniformly fatal outcome of all great vessel injuries is likewise reported by Loria.<sup>14</sup> By great vessel, we refer to femoral artery or vein, iliac artery or vein, cava or aorta.

The gravity of coincidental abdominal and chest injuries is not generally realized. The patients in these cases are in striking contrast to those admitted to our service with perforating injury of chest alone, practically all of whom recover on a conservative regime. As can be seen in Table VII, the mortality of the thirty-four cases in which there



## POSTOPERATIVE EVISCERATION

The incidence of wound disruption in this series is 5.6 per cent, which is extremely high. Bowen<sup>27</sup> and Meleney<sup>28</sup> place the occurrence of this complication at between 0.5 and 1.0 per cent of laparotomies in general. Taylor<sup>13</sup> reports an incidence of 3 per cent among his 101 cases of perforating abdominal gunshot wounds. Fortunately, the mortality of the present group, 26.3 per cent, is somewhat less than the average in the literature, namely about 30 per cent.

All but four of our nineteen eviscerations occurred between the sixth and tenth days; the shortest interval was three days, the longest nineteen. Although dietary data on these patients are not available, they are, as a rule, vigorous, well developed and well nourished and one would be less inclined to suspect them of vitamin deficiency or hypoproteinemia than the average ward patient undergoing laparotomy and in whom the incidence of evisceration is much lower. Massive hemorrhage might reasonably be expected to produce in the survivor severe hypoproteinemia. Yet in only one instance did evisceration follow severe hemorrhage, and only twice did it follow moderate hemorrhage. In the other sixteen cases the blood loss was trivial.

Of the nineteen disrupted wounds, seven were infected. Stay sutures were used in ten (no statement as to stays in five) and only one was drained. Suture material in the majority was chromic catgut, silk was used twice, and through-and-through "Kaldernie" sutures were used once.

The rectus incision was used in the combined gunshot and stab wound series 289 times with a 4.5 per cent incidence of dehiscence as against 16.6 per cent for the transverse incision, which was used eighteen times. This disparity of incidence is maintained if we consider only those cases from 1938, when we began to use the transverse incision, through 1941. During this time there have been fifty-nine rectus incisions with 3.4 per cent of eviscerations, as compared to twenty-six transverse incisions with 15.4 per cent of eviscerations.

Why the incidence of wound disruptions is so high among these cases and especially so among those explored through a transverse incision is an unsolved problem. Perhaps part of the answer is mechanical stress and strain. Many of these patients are intoxicated and uncooperative, often kept in bed only by dint of restraints.

## TREATMENT

*Time of Operation.*—All are agreed that any abdominal injury proved to be penetrating, with the exception of bird-shot or ice-pick wounds, should be explored promptly, but opinion is divided as to the advisability of delaying operation to treat shock. Meyer and Shapiro,<sup>3</sup> Wilson,<sup>6</sup> Storek,<sup>2</sup> Billings and Walking,<sup>16</sup> Loria,<sup>24</sup> and Rippey,<sup>15, 22</sup> advise against operating, if possible until the shocked patient's blood pressure has risen above the critical level. Fleming and McClamroch<sup>14</sup> and Van

## SHOCK IN PERFORATING ABDOMINAL TRAUMA

In this study a patient is considered in shock whose systolic blood pressure is 80 or under. We found, as did Keckwick and co-workers,<sup>22</sup> that the pulse rate shows little correlation with the blood pressure and is a less accurate index of the extent of blood loss and injury. The unreliability of the blood pressure itself in this respect is shown by the thirty-four patients (Table IX) who had suffered marked blood loss with or without severe trauma and who arrived with a systolic pressure above 80.

TABLE IX

CORRELATION OF ADMISSION SYSTOLIC PRESSURES ABOVE AND BELOW SHOCK LEVEL WITH SEVERE TRAUMA, SEVERE HEMORRHAGE, BOTH OR NEITHER

SYSTOLIC BLOOD PRESSURE	SEVERE TRAUMA ALONE	SEVERE HEMORRHAGE ALONE	SEVERE HEMORRHAGE AND TRAUMA	WITHOUT SEVERE HEMORRHAGE NOT TRAUMA
Above 80	0	21	13†	--
80 or lower	3*	18	16†	11

\*Two of these had associated severe chest injuries.

†Six of these with systolic pressure above 80 and five below 80 had associated severe chest injury.

We are becoming increasingly convinced that for all practical purposes in perforating abdominal injury, hemorrhage and shock are synonymous. It will be observed in Table IX that only three patients whose systolic pressure upon entry was 80 mm. mercury or less had sustained severe trauma\* alone. Furthermore, in two of these three instances, shock was explainable by the disturbed physiology of severe coincidental chest injury. Large hemorrhage with negligible trauma was responsible for collapse eighteen times, while large hemorrhage, together with severe trauma, were responsible sixteen times.

In eleven penetrating abdominal wounds and in three nonpenetrating stab wounds, shock was associated with neither appreciable hemorrhage nor trauma and must therefore be explained on a primary or neurogenic basis. The average pulse rate (85 per minute) of patients in primary shock, although varying widely, ranged 17 beats per minute less than that of patients in secondary or surgical shock.

In short, not only does hemorrhage play the chief role in mortality (see again, Tables II, VII, and VIII), but it seems to be the one essential cause of secondary shock. Keckwick and colleagues,<sup>23</sup> in their analysis of traumatic shock in British soldiers, express the belief that circulatory collapse in these cases (chiefly wounds of the extremities) is explainable entirely by the loss of blood and plasma into the damaged area. This is even more true of these abdominal injuries where bleeding into the peritoneal cavity is far more free and unlimited.

\*Under "severe trauma," we have arbitrarily included such damage as ten bowel perforations or more, pulpified kidney, very extensive liver, or pancreatic injury along with other injuries, major coincidental fractures, and severe coincidental thoracic injury.

Furthermore, we feel that blood or plasma should not be withheld preoperatively on the grounds that by raising the patient's pressure it will promote further bleeding. Analysis of the effectiveness of transfusions among our cases is misleading. Of the seriously injured patients, the group that died averaged 725 c.c. blood per patient, while those that lived received 600 c.c. each. Obviously, however, the most desperately wounded died in spite of the larger amount of blood received. Rippey<sup>15</sup> gives the mortality of his large hemorrhage group receiving transfusions as 74.4 per cent, as against 90.7 per cent for those not transfused.

*Autotransfusion*, however, has offered brilliant possibilities since 1935, when our surgical service adopted the policy of returning to the seriously injured patient all free peritoneal blood, contaminated by bowel contents or otherwise, that was not over six hours old. The rationale of this has two simple bases, first the saying familiar to all, "You can't infect the blood stream" and second, "Save this patient now and worry about possible infection later." It is surprising that this practice was not adopted years ago. Meyer and Shapiro,<sup>3</sup> Storek,<sup>9</sup> Billings and Walking,<sup>16</sup> Mason,<sup>31</sup> and others recommend auto transfusion only if it is certain that there is no bowel injury. Trimble<sup>32</sup> considers liver injury a contraindication of the procedure, on the basis of possible toxic autolysates. Van Schaick<sup>29</sup> strongly advocates autotransfusion and reports returning 450 c.c. of blood to a woman with a gunshot perforation of the stomach. This is the only instance we are familiar with in which contaminated blood has been reinfused into the patient.

In an analysis of all autotransfusions given at the Louisville City Hospital, inclusive of those for abdominal injuries, Griswold and Ortner<sup>33</sup> found but one instance in which autotransfusion of contaminated blood appeared responsible for death. In this patient, who had received numerous gunshot perforations of the bowel, autopsy revealed multiple small pulmonary emboli. Due to a technical error the reinfused blood on this occasion had been imperfectly filtered. The great majority of autotransfused patients show little if any deviation from the expected postoperative course.

The technique of autotransfusion is simple<sup>33</sup>: The free blood is aspirated into a citrate-containing trap bottle. This citrated blood is poured through ten thicknesses of gauze into an intravenous outfit for retransfusion.

TABLE XI  
AUTOTRANSFUSIONS

AMOUNT GIVEN (C.C.)	HOLLOW VISCERA INJURED		SOLID VISCERA INJURED*	
	LIVED	DIED	LIVED	DIED
500† to 1000	2	5	6	1
1000 to 2000	2	7	3	1
Over 2000	0	3	1	1

\*In 3 cases omentum or mesentery, and not a solid viscus, was injured.

†Once 300 c.c., and once 100 c.c. blood were given.

Schnick<sup>29</sup> believe that since shock in these injuries is nearly always due to hemorrhage, nothing is to be gained by delaying operation for shock therapy and they recommend that antishock measures be conducted along with surgical intervention. We agree with the latter authors, for we fail to see how blood dribbling into a vein through a needle can compensate for what is meanwhile pouring out into the abdomen through torn vessels.

However, teamwork is important; antishock measures, such as the rapid administration of blood and plasma<sup>26</sup> from the blood bank should not wait upon surgery, but should proceed with it. Thus, by the time the peritoneum is opened a pint of plasma should be well on its way into the vein.

TABLE X  
OUTCOME OF OPERATION UPON PATIENTS STILL IN SHOCK  
(SYSTOLIC BLOOD PRESSURE 80 OR LOWER)

		SEVERE HEMOR- RHAGE ALONE	SEVERE TRAUMA ALONE	BOTH	NEITHER	NOT SPECIFIED	TOTAL
Came out of shock during operation	Lived	5	0	1	10	1	27
	Died	2	0	4	2	2	
Remained in shock through- out operation	Lived	0	0	2	0	0	13
	Died	2	0	8	0	1	

The outcome of patients on whom operation was begun while their systolic pressure was 80 or under (Table X), seems to justify immediate surgery in these patients in whom shock is present. Of the forty cases with available data, only thirteen failed to recover from hypotension in the course of the operation. Furthermore, none of the twelve patients in apparent primary or neurogenic collapse (recorded in Table X as having "neither" severe hemorrhage nor severe trauma) failed to come out of that state during the course of the operation. In this primary shock group, the two deaths, due to bronchopneumonia, could scarcely be ascribed to their having undergone operation while still in collapse, especially as they recovered from it during the procedure. We believe it a fallacy, then, to delay operation for the treatment of secondary shock when operation is the one way of controlling hemorrhage, its cause. On the other hand, operation, gently performed and with intravenous fluids running, will not appreciably aggravate benign or neurogenic shock.

*Transfusion and Autotransfusion.*—The value of transfusion in these cases no longer needs emphasis. Patients in shock or in whom active bleeding is likely, should from the start receive infusions of plasma or blood in so far as it is available in preference to saline and glucose solutions, since the depleted circulation may be dangerously diluted and further plasma proteins lost by too liberal use of the latter (Minot and Blalock<sup>30</sup>).

Furthermore, we feel that blood or plasma should not be withheld preoperatively on the grounds that by raising the patient's pressure it will promote further bleeding. Analysis of the effectiveness of transfusions among our cases is misleading. Of the seriously injured patients, the group that died averaged 725 c.c. blood per patient, while those that lived received 600 c.c. each. Obviously, however, the most desperately wounded died in spite of the larger amount of blood received. Rippey<sup>15</sup> gives the mortality of his large hemorrhage group receiving transfusions as 74.4 per cent, as against 90.7 per cent for those not transfused.

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The thirty-two autotransfusions given in this series are set forth in Table XI. In all but three of the fatal cases death was obviously due to shock and hemorrhage and occurred either on the operating table or within twenty-four hours. The following cases with entirely successful outcome illustrate what a lifesaving reservoir contaminated intra-peritoneal blood may be:

Lacerations of liver	autotransfused 2000 c.c.
Lacerations of stomach and liver	autotransfused 800 c.c.
Bleem perforated 4 times	autotransfused 1500 c.c.
Bleem perforated 12 times	autotransfused 1200 c.c.

We urge that this relatively safe and immediately available source of blood be no longer withheld from critically wounded and exsanguinated patients. To be sure, autotransfusion will not be a necessity where gallons of plasma and blood are available, but how often is this the case either in civil practice or among war casualties?

*Auxiliary Procedures.*—The x-ray and fluoroscope play an important diagnostic role. If the path of a bullet with entry wound only is in doubt, the slug can be localized roentgenologically as the patient is en route to the operating room. The progress of concomitant thoracic injury should be studied by an initial film and later, if necessary, by repeated bedside plates.

Oxygen<sup>34</sup> is administered to patients in shock, either by intranasal catheter or by tent, to combat anoxemia.

Wangensteen suction for decompression of the upper gastrointestinal tract has become a routine for all patients with injury to stomach or bowel. The Miller-Abbott tube is used in case of distention or ileus.

In all cases of peritoneal soiling 10 Gm. of sulfanilamide powder are placed in the abdominal cavity and another 3 to 5 Gm. in the operative incision. More recently, trial is also being made of sulfathiazole and sulfadiazine.

Adrenal cortical extract<sup>35</sup> is probably of some value in combating shock. The synthetic cortical extract desoxycorticosterone acetate<sup>36</sup> since it requires at least six hours to reach its maximal efficiency is of less value in established shock. Our experience with this sterone preoperatively in about fifty major operations has shown no striking prophylaxis against abnormal hypotension and tachycardia when compared to an equal number of control cases. However, our final analysis of this study has not been completed.

*Anesthesia.*—Local anesthesia should not be used in these cases. It is time consuming and must be supplemented in nearly all instances, since adequate exposure and free manipulation of viscera is essential. In the present series spinal anesthesia was employed 165 times with a mortality of 25 per cent and general anesthesia, 151 times, with a mortality of 43 per cent. Since general anesthesia was reserved for the low blood pressure group, which was also the more gravely wounded, this disparity in death rates is not surprising. We feel that the greater relaxation secured by spinal anesthesia more than compensates for its theoretical disadvantage, namely that it stimulates peristalsis and thereby allows

fecal spillage. It is therefore the anesthetic of choice unless contraindicated by low blood pressure.

*Technical Details.*—Thorough discussions of operative principles and details have been presented by Meyer and Shapiro,<sup>3</sup> Storek,<sup>9</sup> and others. Only a few points will be emphasized here.

Abdominothoracic injuries have already been discussed. To avoid overlooking serious intrathoracic injury, repeated portable plates and exploratory thoracenteses should be done in such patients growing worse out of proportion to their abdominal injuries. Aspirated blood not over six to eight hours old should be reinfused into the patient. Tension pneumothorax requires catheter drainage and water trap. If active bleeding continues or the pneumothorax cannot be controlled, thoracotomy should be considered. An initial transthoracic approach is recommended by Gordon-Taylor<sup>37</sup> where the path of bullet or shrapnel crosses the upper abdomen and diaphragm, especially on the left side, a zone which he terms "that fatal left subphrenic area of the abdomen." We have had no experience with this approach but it might prove valuable when significant chest injury as well as upper abdominal injury is suspected at the outset. After the chest lesions are dealt with, the left upper abdomen can be readily explored through the diaphragm.

Abdominal injuries should be approached through an unusually long incision that will allow maximal exposure. We are employing with increasing frequency, the transverse rectus-dividing incision as described by Gurd<sup>38</sup> because its better exposure more than compensates for the high incidence of evisceration. This latter disadvantage we hope to overcome by closing with through-and-through "Kaldernie" or braided silk sutures.

Hemorrhage is to be controlled first and thereafter bowel perforations sutured. Location of bleeders and visceral injuries will be greatly simplified by following the estimated track of the bullet or knife from the entry point in the peritoneum.

It will be found helpful in dealing with active hemorrhage, to apply temporary digital pressure proximally, i.e., compression of the hepatic artery for bleeding from the liver, of the mesenteric or lienal arteries for bleeding from mesentery or spleen, etc.

In the routine examination of the intestine, time and needless manipulation will be avoided by placing a Babcock forceps on the bowel for a marker and "reading" in both directions. Evisceration of more than one loop of bowel at a time during inspection is to be avoided if possible, because of the chilling effect and the drag on the mesentery. A thorough exploration of stomach and bowel is well worth the time spent as it will be recalled that in from 30 to 50 per cent of autopsies, overlooked visceral perforations are found.

If the posterior of two gastric perforations cannot be brought into view through the gastrocolic or gastrohepatic omenta, free enlargement of the anterior perforation will allow satisfactory transgastric exposure and repair (Prey and Foster<sup>21</sup>).

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The kidney region is quickly and easily exposed by incising the avascular lateral colic reflection of peritoneum and reflecting colon and its mesentery mesially.

We agree with Storek<sup>9</sup> that enterostomy proximal to sutured perforations or anastomosis is futile. Satisfactory bowel decompression can be obtained with Wangensteen suction or Miller-Abbott tube.

Abdominal drainage is in most cases useless. However, the kidney fossa and retroperitoneal tissues, if soiled with lower bowel contents, should be drained through a stab wound in the flank. A drain should also be placed if there has been wounding of pancreas or biliary tract, to provide escape for possible leakage of pancreatic juice or bile.

#### SUMMARY

1. One hundred ninety perforating gunshot and 146 perforating stab wounds of the abdomen have been reviewed.

2. The mortality for the entire series is 51 per cent for the bullet wounds and 14.1 per cent for the stab wounds. The operative mortality is 48.9 and 13.8 per cent respectively.

3. These observations and analyses are made:

a. Incidence of vomiting, pain, spasm, and tenderness in non-penetrating as against penetrating injury.

b. The chief causes of death.

c. The effect on mortality of age, time from injury to operation, duration of operation, and amount of blood lost.

d. The various visceral injuries and their mortality.

e. The cause of shock in perforating abdominal injuries. (Primary and secondary shock are differentiated.)

f. The outcome of patients operated upon while still in shock.

g. Postoperative eviscerations.

4. The following points are particularly emphasized:

a. The value of peritoneoscopy in diagnosing peritoneal perforation in doubtful cases.

b. Hemorrhage is synonymous with shock in perforating abdominal trauma and therefore operation to control hemorrhage brooks no delay.

c. Abdominothoracic injury is more serious than generally realized and ameliorable chest injuries are too frequently overlooked or inadequately treated.

d. Autotransfusion, regardless of blood contamination, is urged for all seriously injured patients operated upon within six hours.

5. Treatment is outlined and a few technical details are discussed.

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the lumen was almost completely occluded. There was a regional lymph node hyperplasia and the adjacent mesentery showed small areas of fresh granulation tissue. No other abnormalities were noted. The appendix was removed and both incisions were closed in layers.

Culture of the peritoneal fluid was sterile. Culture of feces following the operation revealed normal intestinal flora. The pathologist's report of the appendix was "no abnormality."

The postoperative course was mild. On the fifth day the temperature became normal and the patient was given a soft diet. He was discharged symptom free on the fourteenth postoperative day.

This patient has been seen on numerous occasions since operation and at no time has he complained of abdominal discomfort of any kind. An x-ray of his abdomen following barium enema in July, 1941, showed the ileocecal valve to be fully patent and the terminal ileum to be well filled. There was no "string sign." This latest checkup was six years and two months after operation. The patient is now considered to be cured.

**CASE 2** (Roper Hospital No 104297).—A 39 year old colored male, a farm-hand, was admitted to the hospital May 26, 1939, complaining of intermittent left lower quadrant pain of three days' duration. The onset was extremely sudden and the pain of a sharp lancinating nature. Prior to the onset of symptoms, constipation was present and only one bowel movement occurred in five days. The patient took castor oil about three hours following onset of acute seizure and promptly vomited. He continued to vomit for twenty four hours, then suddenly stopped, at which time a diarrhea appeared and persisted until admission to the hospital. Meanwhile, the left lower quadrant pain persisted without radiation. There were no urinary, cardiovascular, or respiratory disturbances. Past history was irrelevant except for frequent headaches and intermittent nocturia and frequency, thought to be the result of numerous gonorrheal infections. Examination on admission showed a well nourished negro male to be acutely ill and writhing in pain. Blood pressure was 109/69, temperature, 98° F, and pulse 100 per minute. The abdomen was not distended and moved freely with respiration. Palpation caused exquisite pain over the entire left portion of the abdomen, most marked about 12 inches below and to the left of the umbilicus. There were no masses. Peristalsis was not audible and rectal examination contributed nothing of diagnostic value. The leucocyte count was 10,100 with 85 per cent polymorphonuclears. Urinalysis showed nothing abnormal. No specific diagnosis was made, but exploratory laparotomy was thought advisable.

**Operation**—The abdomen was opened through a left midrectus incision, using spinal anesthesia. There was no appreciable increase in free peritoneal fluid. The proximal four inches of the sigmoid were heavily thickened and indurated and there was a diffuse vascular engorgement of the serosa. Numerous organizing adhesions plastered the sigmoid colon against its mesentery. No evidence of diverticulitis was found. Regional lymph node enlargement was noted. The appendix and remainder of the alimentary canal were normal. Release of the sigmoid by freeing its adhesions was effected, following which the appendix was removed. One enlarged lymph node was removed for study and the abdomen closed in layers. Pathologic diagnosis from sections of the lymph node was chronic lymphadenitis, while the appendix was reported as showing fibrosis.

Recovery of the patient after operation was prompt. The wound healed per primum. On the twelfth postoperative day, an x-ray with the aid of a barium meal revealed the colon to be well filled and showed no abnormalities in the sigmoid region. The patient was discharged symptom free on the thirteenth postoperative day.

Follow up studies of this case have shown the patient to continue in an excellent state of health for two years and two months. A barium enema in July, 1941,

## CONSERVATISM IN THE SURGICAL MANAGEMENT OF ACUTE REGIONAL ENTERITIS

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MUCH has been written in the last few years about regional enteritis and much has been accomplished toward clarifying its puzzling aspects since its original description by Crohn and his associates<sup>1</sup> in 1932. With regard to the acute phase of the disease, surgical treatment roughly divides itself into radical and conservative. The following case reports and discussion of the literature are offered in support of the view that radical treatment is not indicated in those cases of acute regional enteritis initially encountered at laparotomy for an acute abdominal condition. Emphasis is placed upon the fact that the cases and discussion presented below represent that phase of regional granulomatous inflammation of the bowel which is acute or subacute when first seen and which presents clinical findings demanding celiotomy at the time of admission to the hospital.

### CASE REPORTS

CASE 1 (Roper Hospital No. 81503).—A 23-year old colored male, a laborer, was admitted May 18, 1935, with a history of generalized lower abdominal pain, more pronounced in the right lower quadrant, of three days' duration. The pain was intermittent in character and was accompanied by nausea at the onset. Vomiting occurred three times during the first thirty six hours and then stopped. The patient took castor oil at the onset of symptoms and had a watery diarrhea for the next forty eight hours. When he reached the hospital, the discomfort of the patient was entirely confined to the right lower quadrant. There had been no urinary, respiratory, or cardiovascular disturbances at any time. The past and family histories were irrelevant. Examination on admission revealed a well developed negro adult male, obviously acutely ill. The abdomen was flat but did not move with respiration. There was generalized lower abdominal tenderness on palpation which was excruciating over McBurney's point and just below the umbilicus. Rebound pain from left to right was well defined. The right rectus muscle was frankly rigid in its lower half. No masses were palpated. By rectal examination, acute tenderness and suggestive induration were noted high in the right pelvic fossa. Auscultation revealed active peristalsis to be present. Temperature was 102.6° F.; blood pressure 124/66; leucocyte count, 9,950, with 71 per cent polymorphonuclear cells; urinalysis was normal. A diagnosis of acute appendicitis was made.

*Operation.*—Under spinal anesthesia, the abdomen was opened through a Mc Burney incision. A large amount of free serosanguineous fluid was present in the abdominal cavity. Exposure through the gridiron opening was found to be inadequate and a right rectus muscle splitting incision was made. The appendix was normal and was firmly adherent to the ileocecal region by old fibrous bands. The terminal six inches of the ileum were intensely edematous and hyperemic and

month's duration. Pain was said to have been associated with frequent nausea and epigastric fullness but was not accompanied by vomiting. Constipation had been present for some months and there was a marked anorexia. Undue fatigue and slight weight loss developed rather abruptly two weeks before admission. There was no abnormality in the history of the systems. Past and family histories failed to add pertinent data. On physical examination, the temperature was 99.6° F., pulse 85 per minute, and blood pressure 120/80. The abdomen was essentially normal except for pain on deep palpation over McBurney's point. Rectal palpation was normal. The leucocyte count was 14,000 with 78 per cent polymorphonuclears and 8 per cent eosinophiles. Urinalysis was normal except for 1 plus albumin.

A tentative diagnosis of intestinal parasites was made in view of the patient's occupation and the eosinophilia. Several stool examinations, some by special laboratory technique, failed to reveal the presence of parasites or ova. The eosinophilia varied from 6 to 11 per cent. A barium meal and x-ray showed normal stomach and duodenum but a large diverticulum of the jejunum, which retained its barium, was noted. This radiographic study was repeated and similar results obtained. X-rays of the colon after a barium enema and of the thoracolumbar spine were normal. A flat plate of the genitourinary tract was normal.

After the medical department had failed to demonstrate a cause for the eosinophilia, a presumptive diagnosis of jejunal diverticulitis was made and celiotomy advised.

*Operation.*—Using gas-ether anesthesia, a right paramedian incision was made. There was no increase in peritoneal fluid. The jejunum, from the ligament of Treitz to its junction with the ileum, was injected and greatly thickened. Its consistency was soft and boggy. The luminal diameter was reduced. There was a widespread mesenteric lymphadenitis present which was confined to the jejunal mesentery. No abnormality of the other abdominal viscera was noted. The appendix was removed and a lymph node was obtained from the jejunal mesentery for study. The pathologic report from sections of the node was hyperplastic lymphadenitis, and from sections of the removed appendix, no definite abnormality.

The postoperative convalescence on the whole was smooth, but was complicated by separation of the skin edges of the incision after removal of the sutures. Secondary closure healed well. A barium meal was administered on the seventeenth postoperative day and the x-ray showed some clumping of barium in the jejunum but no evidence of stricture was seen. The patient was discharged on the twenty-third day postoperatively. Three recent follow-up visits have found this patient to be rather lethargic and weak. He complains of constant nausea and anorexia but a recent barium radiograph four months after his operation was normal, indicating no progression of the jejunitis toward obstruction or fistula formation. His temperature remains normal and a white blood count made at the time of the last x-ray was 7,500 leucocytes with a normal eosinophile count.

CASE 5 (Roper Hospital No. 118223).—Report of this case is included only to demonstrate the fact that a strong tendency toward spontaneous healing must exist in certain cases of regional enteritis. The case is of too recent origin to be considered cured (see Discussion).

A 27-year-old colored female entered the hospital July 12, 1941, complaining of severe pain in the right lower abdominal quadrant of some twenty hours' duration. At onset, the pain was located in the epigastrium but became localized in the lower abdomen after a few hours. Nausea was pronounced, but no vomiting occurred. One bowel movement early in the illness was effected with the aid of an enema. There were no other symptoms of consequence and the history of the systems was irrelevant. A similar episode was said to have occurred one month previously but disappeared after twelve hours without treatment. Examination revealed a temperature

revealed the sigmoid colon to be normal throughout, showing no spasticity or "string sign" and no diverticula.

**CASE 3** (Roper Hospital No. 110155).—A 21-year old colored male, a hotel bellhop, entered the hospital April 19, 1940, complaining of pain in the right lower abdominal quadrant. Forty eight hours before admission the patient developed a dull gnawing ache in the right half of the abdomen and in the epigastrium. The pain grew steadily worse and vomiting occurred twice shortly after its onset. About twelve hours prior to admission, all discomfort became localized in the right lower quadrant and persisted in that area, undergoing exacerbations and remissions but never completely disappearing. One bowel movement had occurred the day before admission and was described as normal. There was no diarrhea. Nocturnum of moderate degree had been present for several weeks and for three days before entering the hospital the patient suffered some burning on urination unaccompanied by hematuria, dysuria, or passage of stones. The history of the systems was irrelevant and past history totally noncontributory. Examination of the patient showed a well developed colored youth in obvious distress but not acutely ill. Temperature was 100° F., pulse, 92 per minute, blood pressure, 117/70. The abdomen was flat and held motionless during respiration. No abnormalities of the left abdominal quadrants were noted, while the right rectus muscle was rigid and acute tenderness was elicited over McBurney's point. Rebound tenderness was referred from the left lower quadrant to the midline just below the umbilicus. Rectal palpation elicited sharp pain in the right pelvic fossa; there was no mass. The white cell count was 15,000 with 64 per cent neutrophils. The urinalysis was normal. A diagnosis of acute appendicitis seemed inescapable.

**Operation.**—The abdomen was opened through a McBurney incision under ether anesthesia. The appendix appeared innocent and there was considerable free clear peritoneal fluid present. The ileum in its terminal four inches was thickened and intensely hyperemic. Its consistency was boggy. The ileocecal valve was patent but definitely narrowed. There was no involvement of the cecum. A regional lymphadenopathy was present and marked. Culture from the peritoneal fluid was made. A lymph node was excised for study and the appendix was removed followed by inversion of its stump. Pathologic diagnosis from sections of the node was chronic lymphadenitis, etiology undetermined, the removed appendix showed fibrosis only on microscopic study. The peritoneal culture was sterile.

Convalescence of the patient was stormy. He suffered for several days from a watery diarrhea and intermittent, cramping, generalized abdominal pain. Cultures of stools showed normal intestinal flora, no streptococci or dysentery organisms were discovered. A tuberculin test was negative. Gradually, the symptoms subsided and a soft diet was tolerated on the ninth day postoperatively. The wound healed per primam and the patient was discharged on the twenty first postoperative day. Six weeks after the operation, a barium x ray showed normal patency of the ileum and the ileocecal valve but there was considerable irritability of the terminal ileum.

Repeated checkup visits of this patient found him in an excellent state of health and he has offered no complaints of any kind. In August, 1941, barium enema and x ray revealed the terminal ileum to fill normally, there was no encroachment upon its lumen. The patient is considered well fifteen months after operation.

**CASE 4** (Roper Hospital No. 116545).—This case is of too recent origin to be considered a spontaneous cure. It is offered, however, to emphasize the necessity of conservative surgical treatment in that smaller group of patients who present massive involvement of the bowel and so called "skip areas" (see Discussion).

A 21 year old white male, a meat packer, entered the hospital April 16, 1941, with the chief complaint of pain in the right lower abdominal quadrant, of one

roentgen findings during the acute phase other than irritability of the involved segment. The so-called "string sign" belongs to the chronic phase of regional enteritis and makes its appearance quite late in the disease, being dependant upon narrowing of the bowel lumen due to actual fibrosis of the bowel wall. Thus, all x-ray studies of the foregoing cases have been noncontributory as far as verification of the diagnosis is concerned inasmuch as all examinations were made during subsidence of the disease and following recovery. The diagnosis in each instance has been established only after the combined expedients of direct inspection and laboratory exclusion studies.

In reviewing the literature on regional enteritis since its introduction in 1932, one is confronted by the fact that after nine years of study there remains a distinct division of surgical opinion regarding treatment of the acute phase of the disease. Since 1938, however, there appears to have been a definite trend toward conservative management, although proponents of radical measures (enterostomy, resection and short-circuiting procedures) still exist.<sup>2, 3, 4</sup>

The recommendation of conservative treatment (which implies simple exploration with or without appendectomy) must be prefaced by consideration of certain pathologic and clinical features of the disease. To begin with, the etiology of acute regional enteritis is not known. It seems logical to assume that radical manipulation of an acutely inflamed segment of bowel might kindle a smouldering fire into the flaming proportions of peritonitis, even though extensive resection were accomplished. Such a situation is definitely undesirable in a process whose mode of onset and manner of progression are not understood. On the other hand, should the acute disease progress to a chronic state, the treatment of which is undeniably radical resection, the patient can be kept under observation and prepared in advance for an extensive surgical procedure. That progression of the acute state occurs in some instances is well established<sup>4, 11, 12</sup> and the responsibility for its detection is placed directly upon the surgeon who handles his acute cases by conservative methods. Thus, the conservatist is dutifully bound to adopt an organized plan for observation and periodic follow-up examinations, with particular stress upon repeated barium x-ray studies, in all patients treated by laparotomy alone. Proper preoperative management by transfusions, general supportive measures, and some form of enteral chemotherapy, such as sulfanilylguanidine<sup>5, 6</sup> or succinyl sulfathiazole,<sup>7, 8</sup> should take precedence over the choice of radical treatment in an unprepared patient just recently admitted to the hospital. This becomes especially true when one considers that the mortality rate in resection, even under elective conditions, is formidable and that recurrences after resection are reported, varying from Crohn's<sup>9</sup> minimal estimate of 7.7 per cent to as high as 15 per cent.<sup>9</sup>

Spontaneous subsidence of acute regional enteritis, "possibly never to be heard from again,"<sup>10</sup> must be of frequent occurrence. Actual

100° F., pulse 85 per minute, and blood pressure 110/60. The abdomen was flat and failed to move with respiration. Exquisite tenderness was present over the entire right lower quadrant making accurate palpation of deep structures impossible. Rebound pain was intense. Rectal and vaginal examinations elicited extreme tenderness in the right pelvic fossa but no mass could be demonstrated. The leucocyte count was 15,200 with 81% polymorphonuclears. Urinalysis was essentially normal. The diagnosis of acute suppurative appendicitis, possibly with rupture, appeared obvious and operation was advised.

*Operation.*—Under spinal anesthesia, the abdomen was opened through a Mc Burney incision which later had to be extended downward along the right rectus sheath. There was a large amount of dirty, brown, thin fluid free in the abdominal cavity. The cecum, appendix, distal six inches of the ileum, and a large wad of mesentery were inextricably bound together in one large, friable, fixed inflammatory mass which was covered with new granulation tissue and fibrin. On dissecting the mass free, the appendix was noted to be normal while the terminal ileum was bright red, thickened, and covered with granulation tissue. The cecum and proximal three inches of ascending colon closely resembled the terminal ileum and a spontaneous perforation of the cecum one inch in diameter had occurred adjacent to the base of the appendix. The opening had been effectively sealed off within the inflammatory mass. Regional hyperplasia of mesenteric lymph nodes was marked. Further dissection of the friable structures unfortunately resulted in tearing the cecal perforation into a rent of alarming dimensions. Very little gross soiling occurred, however. The appendix was removed and the cecal tear closed with three layers of chromic O catgut. Serosalization of the entire field was impossible due to the marked friability of the tissues. Generous portions of necrotic serosa and fresh granulation tissue were obtained for biopsy study. Sulfanilamide crystals, 10 Gm., were dusted throughout the right lower abdominal quadrant. Penrose drains were placed in the cecal pouch and right pelvic gutter. Closure of the incision was effected in layers with interrupted sutures.

A culture of the peritoneal fluid was negative. Biopsy studies revealed granulomatous inflammatory tissue from the intestine and appendix but failed to uncover any specific etiologic agent. No evidence of tuberculosis was seen in the sections. The appendix showed, on section study, no disease of its mucosa but heavy serosal infiltration by a non-specific chronic inflammatory process.

The patient's postoperative course was satisfactory in every way. The drains were removed on the third postoperative day and soft diet allowed on the fifth day. The wound healed well except for a small sinus persisting at the point of exit of the drains. The patient was discharged on the fourteenth day after operation. The wound sinus healed rapidly. On Sept. 3, 1941, the patient was discharged from the outpatient department symptom free and apparently in excellent health. She is to return at intervals for radiographic study.

#### DISCUSSION

A critical evaluation of the foregoing case reports brings to mind the question of correctness in diagnosis. Clinically, a preoperative diagnosis of acute regional enteritis in a patient seen shortly after the first attack of pain is purely tentative; in the majority of instances the condition is not mentioned among the diagnostic possibilities. Only when celiotomy is performed and direct inspection and palpation of the affected bowel is allowed can one specifically state the existence of acute regional enteritis. Radiographic study of the bowel with the aid of barium is of only limited value in verifying the presence of the disease, in that the acute cases which subside spontaneously give no positive



brief mention of certain of its aspects is included here. Emphasis is given to the fact that appendectomy in acute regional enteritis is purely incidental and not designed to alter the course of the disease *per se*. Tendency to fistula formation is thought by some to be increased by appendectomy in the acute phase. Certainly, the incidence of such is quite low if one depends upon the literature as a gauge. In all cases reported in this series, appendectomy was done, and in Cases 1 and 3 the site of the disease was the terminal ileum, while in Case 5 actual extension to the cecum was present; no fistula resulted in any case. Eliason and Johnson<sup>22</sup> offer the assumption that if the appendix were not removed and later became involved, appendical obstruction due to edema could conceivably take place and early rupture occur. Fallis<sup>33</sup> and Lehman<sup>20</sup> report seven and six cases, respectively, of acute terminal ileitis treated by simple exploration and appendectomy; no fistula occurred.

#### SUMMARY

1. Five cases of acute regional enteritis are reviewed. All were managed by simple exploration and appendectomy and none showed progression of the disease.

2. That a strong tendency toward spontaneous healing is present in certain instances of acute regional enteritis is illustrated by Case 5, in which prompt healing followed primary closure of a perforated cecum in the presence of a very active acute process.

3. Conservative management is mechanically essential in a smaller group of acute cases showing either massive involvement of the bowel or extensive "skip areas."

4. Spontaneous disappearance of acute regional enteritis occurs in a large number of instances, progression to the chronic phase in few.

5. Recurrence after radical resection is relatively frequent, not to mention a formidable mortality rate in patients subjected to radical surgical treatment during the acute phase.

6. In order to detect the occasional case showing a tendency to progress to chronic regional enteritis, conscientious observation and frequent postoperative x-ray study are essential in the acute case managed by simple exploration and appendectomy.

7. Progression from acute to chronic under observation and thorough preoperative preparation by general supportive measures, transfusions, and enteral chemotherapy constitute a far more desirable form of management than radical resection in an unprepared acute case just recently admitted to the hospital.

8. Appendectomy is incidental in the conservative form of surgical treatment; it does not materially increase the risk of fistula formation.

9. If the appendix is not removed at operation, eventual involvement of it by the acute granuloma may cause appendical obstruction from edema with consequent early rupture and peritonitis.

visualization at the operating table of normal bowel previously diseased is reported by Pessagno.<sup>19</sup> Case 5 of this series indicates beyond doubt that a strong healing tendency must exist in some instances of acute regional enteritis, since primary suture of a perforated cecum in the presence of an extensive process brought about healing without fistula formation. Relative proof of the spontaneous disappearance of the acute disease can be had in radiologic study of the bowel at intervals after operation (Cases 1, 2, and 3 of this series). Beyond the phase of x-ray study, one is left only with the patient's symptomatic progress as a guide to evaluating the degree of activity of the disease. The literature offers many reports of spontaneous cure after simple exploration, with or without appendectomy.<sup>13-26</sup> Many of these reports embody case studies representing freedom from symptoms for many years; some include roentgenologic findings. Especially striking are those patients who have remained symptomless for a period of years. Of seven cases investigated by Lehman,<sup>20</sup> two had had no recurrence nine and one-half years after operation (appendectomy) while a third was well after four years. Brown,<sup>27</sup> Rokey,<sup>13</sup> Rixford,<sup>15</sup> Kross,<sup>23</sup> Eliason and Johnson,<sup>22</sup> and Eckel and Ogilvie<sup>24</sup> all have contributed studies of patients, followed for at least four years, who have remained well after conservative treatment. In an all-inclusive review of the world literature, Ravdin and Johnston<sup>28</sup> concluded from their own experience and reports of other authors that extensive surgical procedures are not indicated in acute regional enteritis. They emphasize the fact that a large number of cases subside spontaneously and that in those few which progress to a chronic state, as noted above, careful preoperative management is essential to good results in later resection of the bowel. Direct recommendation for conservative surgical treatment in the acute phase is made by several authors whose writings reflect surgical experience of unusual scope.<sup>29-32</sup> It is interesting to note that Mixer's<sup>12, 32</sup> wide experience has led to a change in his attitude from radical to conservative between the years 1935 and 1939.

There are noted occasionally anatomic features of distribution in certain cases of acute regional enteritis which literally demand that only the simplest surgical methods be employed. In case 4 above, the entire jejunum was found involved at operation, so that radical surgical management was out of the question. Similarly, the occurrence of "skip areas" throughout the intestinal tract provides technical difficulties in resection or short-circuiting which defy the boldest operator. Furthermore, the overenthusiastic surgeon may find that, after removal of an acutely inflamed segment of bowel, a similar acute process exists at a higher level of the alimentary canal. Pitfalls of this nature are eliminated when simple exploration, appendectomy, and closure of the wound are accomplished, to be followed by watchful waiting.

Since removal of the appendix in the presence of an acute granulomatous condition of the intestine has occasioned considerable comment,

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9. If the appendix is not removed at operation, eventual involvement of it by the acute granuloma may cause appendiceal obstruction from edema with consequent early rupture and peritonitis.

visualization at the operating table of normal bowel previously diseased is reported by Pessagno.<sup>19</sup> Case 5 of this series indicates beyond doubt that a strong healing tendency must exist in some instances of acute regional enteritis, since primary suture of a perforated cecum in the presence of an extensive process brought about healing without fistula formation. Relative proof of the spontaneous disappearance of the acute disease can be had in radiologic study of the bowel at intervals after operation (Cases 1, 2, and 3 of this series). Beyond the phase of x-ray study, one is left only with the patient's symptomatic progress as a guide to evaluating the degree of activity of the disease. The literature offers many reports of spontaneous cure after simple exploration, with or without appendectomy.<sup>13-26</sup> Many of these reports embody case studies representing freedom from symptoms for many years; some include roentgenologic findings. Especially striking are those patients who have remained symptomless for a period of years. Of seven cases investigated by Lehman,<sup>20</sup> two had had no recurrence nine and one-half years after operation (appendectomy) while a third was well after four years. Brown,<sup>27</sup> Roeky,<sup>13</sup> Rixford,<sup>15</sup> Kross,<sup>23</sup> Eliason and Johnson,<sup>22</sup> and Eckel and Ogilvie<sup>24</sup> all have contributed studies of patients, followed for at least four years, who have remained well after conservative treatment. In an all-inclusive review of the world literature, Ravdin and Johnston<sup>28</sup> concluded from their own experience and reports of other authors that extensive surgical procedures are not indicated in acute regional enteritis. They emphasize the fact that a large number of cases subside spontaneously and that in those few which progress to a chronic state, as noted above, careful preoperative management is essential to good results in later resection of the bowel. Direct recommendation for conservative surgical treatment in the acute phase is made by several authors whose writings reflect surgical experience of unusual scope.<sup>29-32</sup> It is interesting to note that Mixer's<sup>12, 32</sup> wide experience has led to a change in his attitude from radical to conservative between the years 1935 and 1939.

There are noted occasionally anatomic features of distribution in certain cases of acute regional enteritis which literally demand that only the simplest surgical methods be employed. In case 4 above, the entire jejunum was found involved at operation, so that radical surgical management was out of the question. Similarly, the occurrence of "skip areas" throughout the intestinal tract provides technical difficulties in resection or short-circuiting which defy the boldest operator. Furthermore, the overenthusiastic surgeon may find that, after removal of an acutely inflamed segment of bowel, a similar acute process exists at a higher level of the alimentary canal. Pitfalls of this nature are eliminated when simple exploration, appendectomy, and closure of the wound are accomplished, to be followed by watchful waiting.

Since removal of the appendix in the presence of an acute granulomatous condition of the intestine has occasioned considerable comment,

## OPERATIVE CHOLANGIOGRAPHY

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### CHOLANGIOGRAPHY DURING OPERATION

ONE of the chief problems of gall bladder surgery has to do with exploration of the common duct. If no stones are in the common duct, it is best to leave it alone; if stones are present, it is essential to remove *all* of them. Every surgeon of large experience knows that it is often difficult to tell whether stones are present and even more difficult at times to tell whether all stones present have been removed.

Our criteria for internal exploration of the common duct during the operation have been (1) patient jaundiced at time of operation, or a history of jaundice; (2) palpable stones in common duct; (3) dilated common duct.

With these criteria we find that in our last 500 cholecystectomies we have opened the common duct forty-five times or 15 per cent. In about one-third of these instances no stones were found, that is, in those cases it would have been better had we let the common duct alone. We do not think debris or so-called "sand" which can be scooped out of any common duct when the gall bladder itself contains "sand" has any special significance or requires mechanical removal. Experience has shown us again and again that the fact that a probe can be passed with ease through the common duct into the duodenum is not an absolute sign that no stone is present in the duct. In a dilated common duct a stone of large size can lie in the lumen and not come in contact with the probe at all as it makes its way through the duct. Even when the duodenum is mobilized, a procedure we use with great frequency, the stone may not be palpable without or with a probe in the duct.

In one instance that we know of for a certainty we did not remove all of the stones which were present in the common duct but left one behind. The patient in question died of a pulmonary embolus on the tenth day of an apparently excellent postoperative convalescence. At autopsy the overlooked stone was found lying free in the common duct. We had exercised every possible precaution at the time of operation, had palpated the duct inside and out, had flushed out the duct, passed probes through the duct into the duodenum and had probed up into the hepatic ducts, yet here at autopsy was the stone the size of a large pea, mute but absolute evidence that the methods at our command were inadequate for obtaining

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The cystic duct is isolated as if for ligation and a ligature passed around it. A small slit is made into the duct and a ureteral catheter threaded into the cystic duct and through it into the common duct. The ligature is then tied with a single knot around the cystic duct just proximal to the opening, tightly enough to hold the catheter in place but not tightly enough to constrict it. From 5 to 20 c.c. of a sterile solution of skiodan and acacia (this is a stock preparation) are injected through the catheter into the duct.



Fig. 2.—Actual immediate cholangiogram showing three radiolucent stones. Note the cystic duct through which, in this case, the common duct was injected; the common duct is slightly dilated. Note the spill into the duodenum through the patent ampulla of Vater. For the sake of clearness the upper part of the film showing the branching of the hepatic radicals of the biliary tree is not shown.

The operative field is covered with a sterile sheet and the portable x-ray machine wheeled into place and centered.

The respiration of the patient is checked by producing a temporary apnea by means of a high oxygen concentration if the patient is having a general anesthesia, or by simply having the patient hold his breath if the operation is being done under spinal anesthesia.

an accurate knowledge of whether or not stones were present in the duct. In the hope of reducing, if not completely eradicating, the possibility of repeating such a mistake we have for the last two years made use of cholangiography during operation wherever we thought indicated. As we have become more familiar with this procedure our indications have increased and we now use immediate cholangiography whenever we feel that there is the slightest doubt that a common duct stone may be present

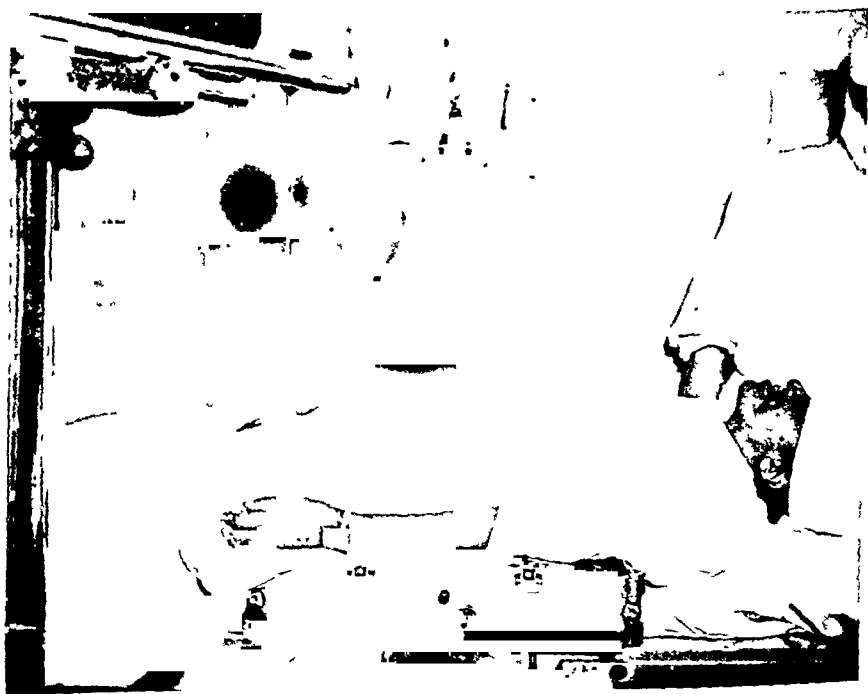


Fig. 1—Method of placing patient on table. Note the Bucky diaphragm and the pads above and below so that the patient lies comfortably on a plane.

Our technique is as follows. We have secured for the operating room a portable x-ray machine which is spark proof and which has no high tension cables which are exposed. We have a small Bucky diaphragm which can be placed on the operating table and which contains a tunnel for the plate. The Bucky diaphragm is so placed upon the table that its center will roughly underlie the site of the patient's common duct. The rest of the table is built up with heavy pads so that the patient lies comfortably (Fig. 1). The operation proceeds as usual except that lap towels are held in place by suture and that all subcutaneous bleeders are immediately ligated, thus doing away with towel clamps and hemostats which would interfere with the roentgenogram. After the gall bladder and ducts have been exposed the common duct is carefully palpated as usual with the index finger in the foramen of Winslow. If we decide that a cholangiogram is indicated we proceed as follows:



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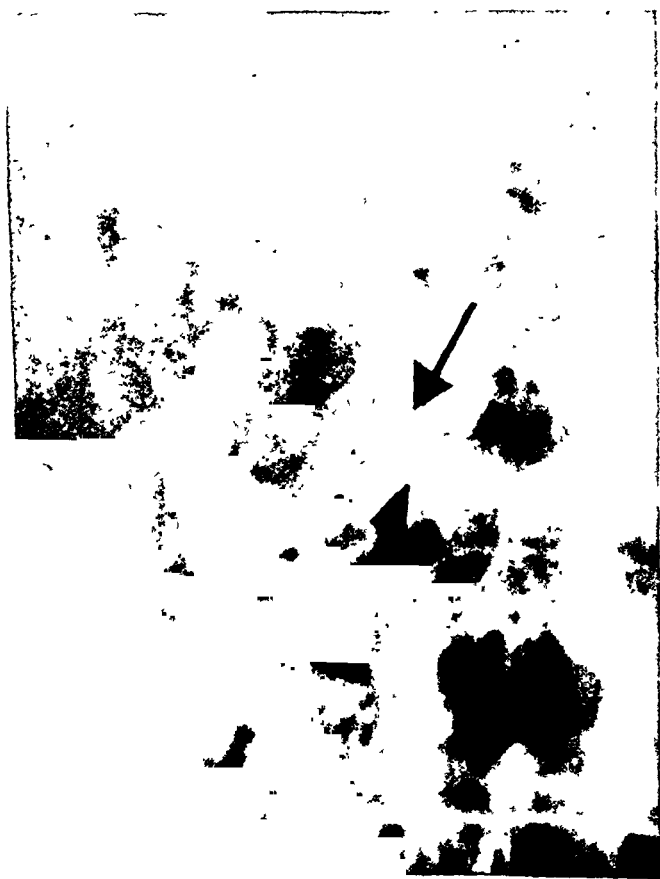


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The roentgenogram is taken and immediately developed in a neighboring darkroom using high-speed developers and fixatives. In less than three minutes the film is ready for viewing. Very frequently a second roentgenogram is taken to see how much of the injected media has escaped into the duodenum.



Fig. 3.—Delayed cholangiogram taken through T tube to show the ramifications of the biliary tree and the normal size relationship of the common duct.

The interval between exposures is used for general intraperitoneal exploration, removal of the appendix, when this is to be done, isolation of the cystic artery, etc. If the cystic duct is obstructed, as of course not infrequently happens, the skiodan and acacia are injected directly into the common duct with a syringe and fairly short pointed needle. Unless the common duct is very thin because of great distension the contrast media will not leak back through the puncture hole. If the common duct is greatly distended we frequently first aspirate much of the contained bile and then inject. The puncture wound can be clamped if it should leak.

The reading of the plates is an art and we realize that we are far from proficient. We realize, however, that as time goes on and we gain more and more experience the interpretation of the plates becomes easier. Frank normals are unmistakable, as are those in which the stones show

clearly. Air bubbles can be fairly easily differentiated from stones. At first we purposely injected small amounts of air during the second exposure to see whether or not air bubbles might be confusing. Edema near or at the ampulla of Vater is occasionally difficult to distinguish from actual stenosis.

In the case of multiple stones it is a great comfort to the surgeon when he finds that the number he has removed from the duct tallies with the number on the plate.

We have had no ill results from this procedure nor see why there should be any.

We have in the last two years had one experience of finding a stone which otherwise would have been overlooked. This was a patient in whom three stones, two large and one small, were seen on the cholangiogram and only the two larger ones could be palpated and were removed. Because of the third negative shadow on the film we persisted in our search and finally flushed out the smaller stone (Fig. 2). We have in several instances felt confident in the presence of a normal cholangiogram that we were correct in our decision not to open the common duct where otherwise we might have been skeptical (Fig. 3). The prolongation of the operation has been slight and we think absolutely justifiable.

After having availed ourselves of the procedure of operative cholangiography we find it difficult to understand why it is so infrequently used. We heartily agree with these authors who advocate it and we predict that within a few years it will be universally adopted.

# THE EFFECT OF LIGATION OF ARTERIES OF THE STOMACH UPON ACID GASTRIC SECRETION AND UPON THE ENDOSCOPIC APPEARANCE OF THE GASTRIC MUCOSA IN THE DOG\*

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AMONG the factors acting in the production of peptic ulcer, the so-called "circulatory factor" has received considerable attention. It has been demonstrated that acute experimental ulcers may be produced by causing embolic or thrombotic occlusion of the small gastric vessels. In rabbits and dogs, however, Graulich<sup>2</sup> and others have found that simple ligation of the large vessels fails to produce ulceration. This observation is particularly important to the gastric surgeon who must interfere with the blood supply to the stomach in the course of operative procedures. In an attempt to secure further information on this subject we have carried out a series of experiments in dogs to study the effect of ligation of arteries of the stomach upon acid gastric secretion and upon the endoscopic appearance of the gastric mucosa.

## METHOD OF EXPERIMENTATION

Healthy adult dogs were used in this study. They had been maintained on the standard laboratory diet for four weeks before the experiments were undertaken. During this period three control measurements were made of the acid gastric secretory response to the subcutaneous injection of 1.5 mg. histamine phosphate, and gastroscopic examinations were performed to ascertain that the mucosa appeared normal.‡

Various arteries of the stomach then were divided between double ligatures and the effects of the operations upon acid gastric secretion and upon the endoscopic appearance of the gastric mucosa were studied (Tables I and II). All operative procedures were carried out under pentobarbital-sodium anesthesia and with aseptic technique. In all of the animals the position of the pylorus was changed according to Layne's technique<sup>3</sup> in order to permit satisfactory gastroscopic visualization of the stomach.

\*This work was supported by a grant from the Medical Research Fund of the Graduate School, University of Minnesota.

†Dr. Layne is now associated with the Great Falls Clinic, Great Falls, Montana.

‡The technique for gastroscopic examination of the dog has been described previously.<sup>3</sup>

In eight dogs various combinations of arteries to the stomach were interrupted (see Table I and Fig. 1), avoiding injury to the accompanying veins. In a ninth animal the greater curvature of the stomach was devascularized completely and the spleen was removed. The animals recovered promptly and were observed for periods of from 24 to 229 days after operation. Gastroscopic examinations were performed immediately after operation and then at weekly intervals. Acid gastric secretion in response to histamine was measured at frequent intervals (see Table I).

Three of the animals in the first series (Dogs 3, 4, and 6) were used later in further experiments and all of the remaining large arteries to the stomach were ligated (see Table II). In order to effect a more nearly complete devascularization of the stomach, the splenic vessels were ligated and the spleen was removed. In Dog 3, the hepatic artery was ligated at the final operation, but in Dogs 4 and 6 the hepatic artery was not injured. In three additional dogs (10 to 12) all of the branches of the celiac axis except the hepatic artery were divided between ligatures and the spleen was removed (Table II). Gastroscopic examinations were performed before and immediately following the operation. Acid secretion was normal in these animals prior to the vascular ligation, but was not studied after operation because the survival period was short.

All animals were examined after completing the experiments to ascertain that interruption of the vessels had been effected.

#### OBSERVATIONS

Ligation of two or three of the large arteries to the stomach produced no significant alteration of the acid gastric secretion (Table I). Neither did it change the appearance of the mucosa as viewed through the gastroscope, except for a transient hyperemia observed immediately following operation in several animals. Such hyperemia may be observed following simple manipulation of the stomach (Layne<sup>3</sup>). Gastric mucosal erosions, hemorrhages, or ulcerations were not observed in any case. Even complete devascularization of the greater curvature (Dog 9) failed to change the acid gastric secretion or the endoscopic appearance of the mucosa. Microscopic sections of the gastric wall were prepared in three cases (Dogs 5, 8, and 9, which were sacrificed after 154, 58, and 58 days, respectively), and these showed no pathologic change resulting from the experimental procedures.

Ligation of all four of the main arteries to the stomach resulted in death of the animals (Table II). Death occurred whether the arterial occlusion was carried out in one (Dogs 10, 11, and 12) or two stages (Dogs 3a, 4a, and 6a). Two of the animals (Dogs 6a and 12) survived for less than ten hours. They showed many mucosal hemorrhages but

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TABLE I  
THE EFFECT OF DOUBLE LIGATION AND DIVISION OF TWO OR THREE ARTERIES OF THE STOMACH UPON ACID GASTRIC SECRETION AND UPON THE ENDOSCOPIC APPEARANCE OF THE GASTRIC MUCOSA OF THE DOG

Dog No.	Number of Arteries Ligated	Arteries Ligated	Number of Days Observed After Ligation	Effect of Ligation of Gastric Arteries upon Acid Gastric Secretion						Effect of Arterial Ligation upon Appearance of Gastric Mucosa
				Free Acid			Total Acids			
				20 Min.	40 Min.	60 Min.	20 Min.	40 Min.	60 Min.	
1	2	Right gastric, right gastro-epiploic	Control period	36.0 57.8 48.9	65.0 69.0 56.0	68.5 62.0 —	45.0 62.9 53.0	69.9 74.0 61.0	72.0 64.5 —	No change
			14 24	53.4 51.2	70.6 60.7	— 63.0	62.8 59.9	79.9 70.0	— 72.1	
2	2	Right gastric, left gastric	Control period	60.8 61.2 48.3	59.0 69.0 34.5	9.0 26.9 —	68.0 66.6 54.1	64.1 78.0 40.0	11.7 34.4 —	No change
			2 5 12 23 29	50.1 21.3 55.7 52.0 44.4	43.5 58.0 61.4 78.5 58.9	58.4 45.3 61.8 72.9 28.4	59.5 30.7 67.0 56.9 50.9	56.5 64.4 72.3 82.5 63.5	69.9 51.9 76.5 77.0 33.2	
3	2	Left gastric, left gastro-epiploic	Control period	43.5 29.2 33.7 21.4	53.1 54.0 28.5 40.7	23.9 46.0 — 29.2	52.2 39.0 41.6 28.8	61.4 62.3 34.5 48.4	28.4 50.2 — 38.9	No change
			4 25 32 46 53 74 165	54.0 46.2 37.4 64.5 45.2 78.0 42.5	96.5 57.0 10.8 57.2 43.0 41.5 23.0	77.0 49.0 — — 33.0 —	63.0 52.5 46.2 71.8 50.0 83.5 47.8	105.6 64.7 17.8 65.1 49.6 48.5 27.3	84.3 55.5 — — — 39.3 —	

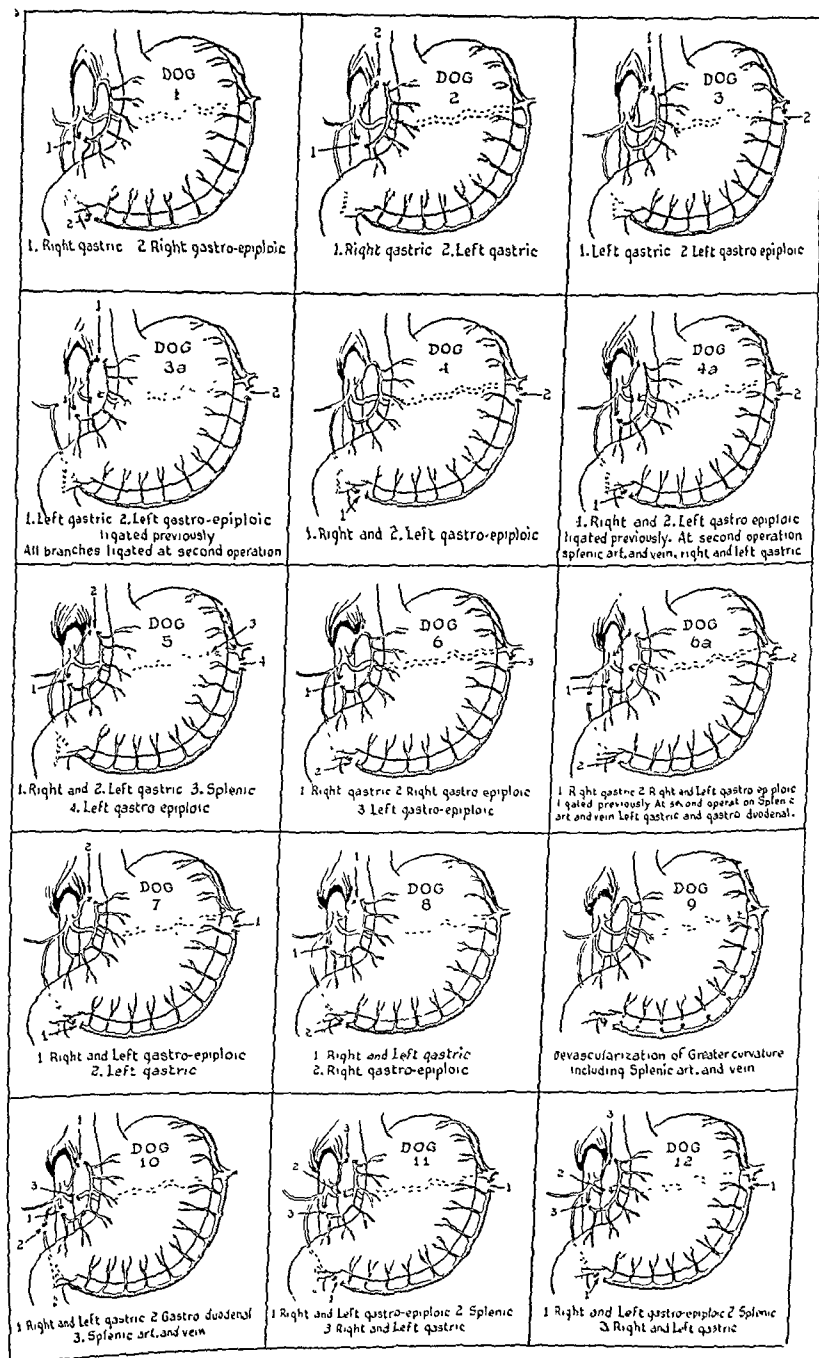


Fig. 1.—Schematic representation showing the arteries of the stomach which were ligated in the twelve dogs used in this experiment. The numbers identifying the animals correspond with those in Tables I and II.

7	3	Left gastric, left gastro-epiploic, right gastro-epiploic	Control period	34.3 19.8 32.6	59.1 50.0 41.2	49.0 — 32.0	39.1 27.5 38.0	69.8 57.4 47.5	59.5 — 39.5	No change
			14	21.1	43.6	10.0	26.0	48.8	16.0	
			21	44.6	55.9	—	52.0	63.0	—	
			35	52.4	67.5	39.0	60.0	75.4	47.0	
8	3	Left gastric, right gastric, right gastro-epiploic	Control period	68.2 112.0 92.1	88.2 126.0 104.0 122.0 124.5	80.0 120.1 128.7 105.0 122.2 118.1 76.1 116.0	— — — — — — — —	76.1 124.0 102.0 96.7 134.0 114.4 128.1 80.3 130.0	96.6 132.4 132.1 112.2 128.1 126.0 80.3 124.7	No change
			8	—	—	—	—	—	—	
			15	—	—	—	—	—	—	
			25	—	—	—	—	—	—	
			34	—	—	—	—	—	—	
			49	—	—	—	—	—	—	
9	2	Devascularization of the entire greater curvature—arteries and veins; splenic artery and vein	Control period	116.6 112.0 98.2	116.6 112.0 98.2	128.0 62.0 18.7	— — —	122.0 128.4 112.3	138.2 74.7 32.1	No change
			6	94.4	94.4	74.0	—	108.8	85.0	
			15	120.0	120.0	100.5	—	126.0	110.6	
			25	120.8	120.8	10.6	—	126.9	25.0	
			34	118.0	118.0	80.8	—	122.7	92.0	
			39	116.2	116.2	20.7	—	122.0	28.8	



3	Left gastric, left gastro epiploic, right gastro epiploic	Control period 11 21 35	31.3 19.8 32.6	59.1 30.0 41.2	39.0 — 32.0	39.1 27.5 38.0	69.8 57.4 47.5	59.5 — 39.5	No change
3	Left gastric, right gastro epiploic	Control period 11 21 35	21.1 14.6 52.4	43.6 55.9 67.5	— 39.0	26.0 52.0 60.0	48.8 63.0 75.1	16.0 — 47.0	No change
3	Left gastric, right gastro epiploic	Control period 8 15 25 31 49	68.2 112.0 92.1	88.3 126.0 104.0 122.0 121.5	80.0 120.1 128.7	96.7 124.0 114.4 128.1 130.0	96.6 132.4 132.1	112.2 128.1 126.0 80.3 121.7	No change
3	Devascularization of the entire greater curvature and veins; splenic artery and vein	Control period 6 15 25 31 39	116.6 112.0 98.2	128.0 62.0 18.7	122.0 128.4 112.3	138.2 74.7 32.1	122.0 128.4 112.3	85.0 110.6 25.0 92.0 28.8	No change

TABLE I  
THE EFFECT OF DOUBLE LIGATION AND DIVISION OF ALL FOUR OF THE MAJOR ARTERIES OF THE STOMACH IN THE DOG

DOG NO.	ARTERIES LIGATED PREVIOUSLY	INTERVAL BETWEEN FIRST OPERATION AND COMPLETE VASCULAR LIGATION (DAYS)	ARTERIES LIGATED AT FINAL OPERATION	SURVIVAL TIME (HOURS) FOLLOWING COMPLETE LIGATION OF THE STOMACH	GASTROSCOPIC EXAMINATION		NECROPSY FINDINGS FOLLOWING COMPLETE ARTERIAL LIGATION OF THE STOMACH
					BEFORE OPERATION	AFTER COMPLETE ARTERIAL LIGATION	
3a	Left gastric, left gastro-epiploic	174	All branches of celiac axis including hepatic; splenic artery and vein	10	Normal	Mild generalized pallor of the mucosa	A diffuse peritonitis was present, the middle two-thirds of the stomach was gangrenous, the liver was dark and congested
4a	Right gastro-epiploic, left gastro-epiploic	53	Splenic artery and vein, right and left gastric arteries; hepatic artery left intact	16	Normal	Mild generalized pallor	A generalized peritonitis was present, the middle two-thirds of the stomach was gangrenous
6a	Right gastric, right gastro-epiploic, left gastro-epiploic	246	Splenic artery and vein, left gastric artery, gastroduodenal artery; hepatic artery intact	6	Normal	Moderate pallor of all of the mucosa; several fresh mucosal hemorrhages along the middle part of the lesser curvature	The stomach was dilated, there were numerous submucosal hemorrhages along the greater curvature, there were no ulcerations or perforations of the stomach; the peritoneal surfaces were smooth
10			Left gastric, right gastric, gastroduodenal, splenic artery and vein; hepatic artery intact	36	Normal	Pallor of the mucosa in the middle two-thirds of the stomach	Generalized peritonitis, almost complete necrosis of middle three-fourths of the stomach
11			Left and right gastro-epiploic arteries, left and right gastric arteries, splenic artery and vein; hepatic artery intact	20	Normal	Not performed	Generalized peritonitis, gangrene of the middle three-fourths or more of the stomach
12			Left and right gastro-epiploic arteries, left and right gastric arteries, splenic artery and vein; hepatic artery intact	8	Normal	Mild generalized pallor	Many mucosal hemorrhages were present; there were no ulcerations or perforations of the stomach, peritoneal surfaces were smooth

no necrotic areas. The remaining four dogs survived for periods of 10, 16, 20, and 36 hours. They developed gangrene of the middle two-thirds to three-fourths of the stomach and a generalized peritonitis. Five of the six animals in the second series (Table II) were examined gastroscopically immediately after completion of the operation. In these a pallor of the mucosa was observed, most marked in the middle two-thirds of the stomach. Further gastroscopic examinations were not carried out because of the short survival time of the animals.

#### DISCUSSION

Lithauer<sup>4</sup> stated that the blood supply to one-third of the stomach could be cut off without producing deleterious effects. Graulich<sup>2</sup> and others also noted the absence of ulceration after ligation of various vessels supplying the stomach. Our studies confirmed this observation, and demonstrated that the gastric mucosa appeared normal when two or three of the large arteries to the stomach were ligated. Schindler, Necheles, and Gold<sup>5</sup> stated that ligation of various arteries supplying the stomach did not produce significant pathologic changes in acute experiments with dogs. (Their report does not state which arteries were ligated in individual experiments.) They stated further, however, that when the gastric mucosa was exposed to the action of  $\frac{N}{10}$  hydrochloric acid or acid gastric juice stimulated by the administration of drugs, ulcerations and hemorrhages occurred in the devascularized portions, but not in the areas in which the blood supply had been left intact. In our animals no erosions or ulcerations were observed. Acid secretion remained approximately at preoperative levels, and no attempt was made to increase it except for the transient effect of the histamine phosphate injected for the purpose of measuring the acid secretory curve at intervals during the period of observation (Table I).

Our results also demonstrate that sudden, complete occlusion of the celiac axis or of the four large arteries to the stomach produces death of the dog. Blalock and Levy<sup>1</sup> have been able to produce gradual, complete occlusion of the celiac axis and superior and inferior mesenteric arteries in dogs without causing death or permanent injury. No abnormalities of the abdominal viscera were noted in their animals. The effect of the procedure on acid secretion was not studied. Neither was it studied in our animals because the survival period was too short.

#### SUMMARY

1. Ligation of two or three of the large arteries supplying the stomach produced no significant alteration of acid gastric secretion in the dog. Neither did it change the appearance of the gastric mucosa as viewed through the gastroscope.

2. Ligation of the four large arteries of the stomach of the dog resulted in death of the animal within six to thirty-six hours. Necrosis

of the middle two-thirds to three-fourths of the stomach and generalized peritonitis occurred in the animals surviving for ten hours or more.

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# FEMORAL HERNIA

## DESCRIPTION OF A NEW OPERATIVE PROCEDURE

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THE operative treatment of femoral hernia has stimulated the interest and resourcefulness of surgeons for many years. In the constant additions to the literature concerning the repair, two methods of approach have become standard, each of which has its staunch supporters.

One method entails the exposure and repair of the hernia from below Poupart's ligament, the other from above. Besides the difference in approach, the methods of repair differ in other respects and descriptions of procedures number well over 100. Unfortunately, follow-up studies rarely accompany these publications.

As in all operative procedures in which there are two fundamentally different methods, neither one is wholly ideal and each has features which commend it. The ideal would be an operation which combines the best features of the two approaches. Such a method has been suggested by some surgeons but by others it is considered either impossible or too difficult to undertake.

A thorough search of the literature fails to reveal a description of the repair of a femoral hernia which is here recorded and which, it is believed, combines the better features of the two standard types of operative procedure.

### OPERATION

An incision is made directly over the lower border of Poupart's ligament starting at the pubic spine and extending two-thirds of the distance to the anterior superior iliac spine. The wound is deepened and the lower border of the external oblique fascia cleaned, after which the dissection is continued down to the saphenous opening. Here the hernia is freed of its superficial layers and the peritoneal sac opened. This sac is dissected free and pulled down to a point where a high ligation can be done. After ligation the sac is excised and the stump allowed to retract.

All fat and areolar tissue is now carefully removed until the femoral canal and ring are in full view. Dissection with gauze brings Cooper's ligament into the field as a glistening structure of great strength along the ramus of the pubis.

Poupart's ligament is now retracted toward the umbilicus with a small curved retractor which at the same time serves to depress this

ligament. A gauze pad beneath the tip of the retractor protects the peritoneum from injury. The sutures, usually three in number, are passed through Cooper's ligament before being introduced through Poupart's. A small, full curved needle with a cutting edge has been found best for this purpose. The first suture is taken through the outer edge of Cooper's ligament very near the pubis and should include Gimbernat's ligament. A deep bite brings the needle out on the inner side of the ligament where it is pulled through and left on the suture. (See Fig. 1, 1.) If the surgeon encounters difficulty in placing this

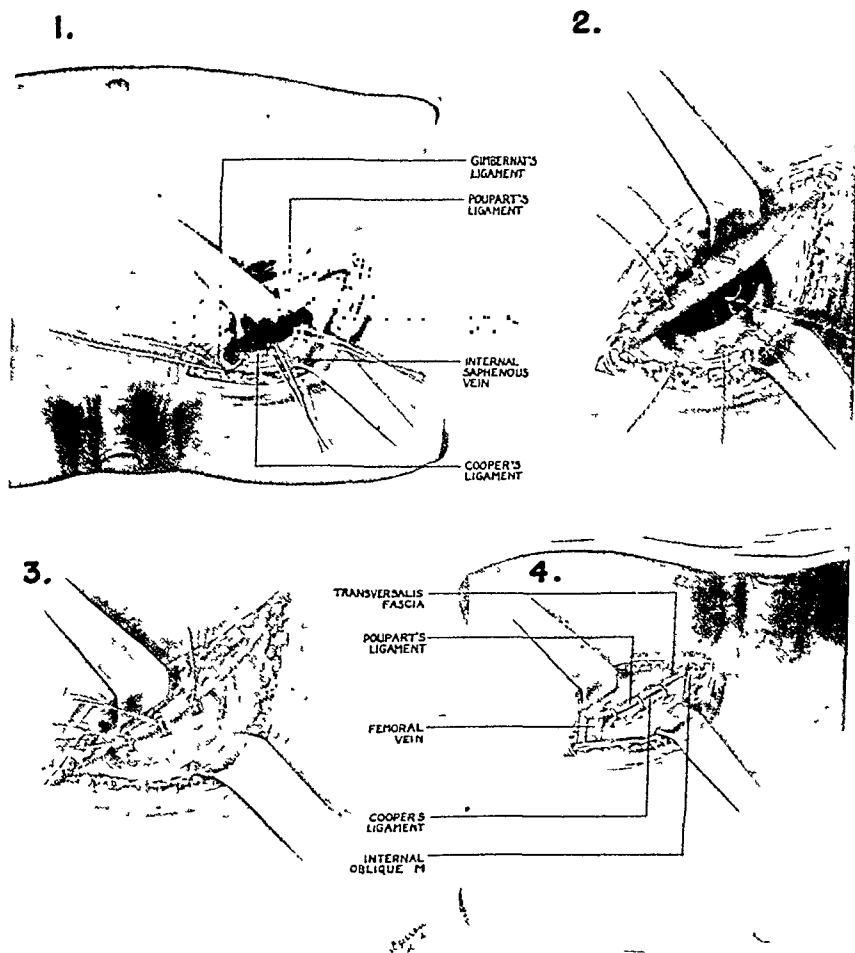


Fig. 1—1. The sutures have been placed through Cooper's ligament. Poupart's ligament is depressed and retracted with a small curved retractor. 2. The sutures are passed through Poupart's ligament, taking a broad, shallow bite. 3. Upon tying the sutures the femoral ring is completely obliterated. 4. An incision has been made through the entire abdominal wall to permit inspection of the repair of the femoral hernia from above; looking at it from this aspect, it is seen to have closed the femoral ring as snugly as though the sutures had been placed from above Poupart's ligament.

suture he may find it easier to accomplish from the far side of the operating table. The last of the sutures should be close to the femoral vein but not so near as to compress this vessel.

Each needle, still threaded on the suture through Cooper's ligament, is now passed through Poupart's, but this time from inside outward. (See Fig. 1, 2.) In this instance a broad shallow bite is taken of the lower margin of the ligament. If a deep bite be taken there is danger in the male of including the spermatic cord in the suture.

Starting with the medial suture each is tied separately, bringing Poupart's into contact with Cooper's ligament and snugly closing the femoral ring. (See Fig. 1, 3.)

Additional sutures of finer material are used to unite the lowermost border of the external oblique to the pectineal fascia and thus reinforce the repair by closing both openings of the femoral canal.

The superficial fascia is closed, the skin approximated, and a light dressing applied. After remaining in bed for a period of two weeks, the patient is allowed up progressively.

Silk is preferred as suture material for this repair.

*Personal Experience.*—This method of repair of a femoral hernia has been used upon numerous cadavers without difficulty and, when inspected by way of the inguinal canal (see Fig. 1, 4), is seen to have closed the ring as completely as when repaired from above by the standard method. The operation also has been performed on both male and female patients without difficulty. Although end results on the patients are not yet available, the immediate results are most gratifying.

*Anatomy.*—A knowledge of the anatomy of the femoral canal and ring is most important in repairing a hernia in this region. Cooper,<sup>1</sup> in 1804, did much to clarify the understanding of the anatomy by publishing his studies and first described the ligament which bears his name.

On the medial side the femoral ring is bounded by Gimbernat's ligament; on the outer side lies the femoral vein; the anterior portion of the ring is formed by Poupart's ligament, and the posterior aspect or floor is formed by Cooper's ligament, which covers the ramus of the pubis. This ligament gives rise to the pectineal fascia and muscle.

#### PREVIOUS OPERATIONS FOR FEMORAL HERNIA

Bassini,<sup>2</sup> in 1894, wrote what still remains the outstanding paper on femoral hernia. In it he describes his operation for repair, carried out below Poupart's ligament. After ligating the sac and freeing the surrounding structures of all loose areolar tissue, he used three or four interrupted sutures to unite Poupart's ligament to the pectineal fascia. Several additional sutures then closed the falseiform process of the fascia lata. He operated in this manner 54 times upon 51 patients,

the hernia being bilateral in three. The course of all patients was without fever or complication. All cases were followed after operation and all were without recurrence; 29 cases for from 3 to 9 years; 14 from 2 to 3 years; 5 from 12 to 18 months, and 4 less than 6 months after operation. Bassini's record has yet to be equalled.

Annandale,<sup>3</sup> in 1876, employed the inguinal approach for the repair of femoral hernia; the only case reported had a recurrence. In 1907, Mosehkowitz<sup>4</sup> described the operation of uniting Poupart's to Cooper's ligament carried out through an inguinal approach and reported eighteen cases repaired in this manner without a recurrence. Ferguson<sup>5</sup> described his operation for femoral hernia in 1895, one year after Bassini's publication; the two procedures are very similar. Cushing,<sup>6</sup> in 1888, reported one case closed from below Poupart's ligament by means of a single "quilted suture," uniting Poupart's to the pectineal fascia. Other authors who have contributed to the literature, describing modifications of the two standard operations, are Lotheissen,<sup>7</sup> Dickson,<sup>8</sup> and Andrews.<sup>9</sup>

*Follow-up Reports.*—McClure and Fallis<sup>10</sup> report 90 cases of repair of femoral hernia. Their study shows a recurrence rate of 9.7 per cent in patients whose hernia was repaired by the femoral route and 7.4 per cent for those repaired by the inguinal route. Shelley,<sup>11</sup> in 222 femoral hernias repaired from below Poupart's ligament, found a recurrence rate of 3.6 per cent. Watson<sup>12</sup> reports 19 recurrences in 469 operations by the femoral route (4.05 per cent) and 10 recurrences in 206 operations by the inguinal route (4.85 per cent).

*New York Hospital Experience.*—At the New York Hospital from September, 1932, through November, 1940, a repair of femoral hernia was carried out 121 times upon 113 patients. An interval of at least six months since the last of these operations permits a review of end results. Follow-up since operation has been impossible in only two cases. The remainder have all been seen personally in the surgical follow-up clinic and examined there by a member of the surgical department.

Of the 113 patients, 95 were women and 18 men. Of the hernias, 100 occurred in female and 21 in male patients. Hernias presented on the right side in 84 instances and on the left in 37. In 5 patients the hernia was bilateral.

The ages of patients ranged from 15 to 79 years of age in the female and from 10 to 66 in the male. The duration of the hernia preceding operation varied from 1 day to 32 years.

At the time of the first operation in this hospital, 4 hernias were recurrent while five, recurring after operation here, were again subjected to operative treatment. Therefore, 9 recurrent hernias are included in this report. To date, only 1 of this group has recurred.

In 10 cases the hernia was strangulated but in only 1 was a resection of the bowel necessary.

At the time of operation associated conditions included varicose veins in 6 and diabetes mellitus in 2, while hypertension, syphilis, goiter, pernicious anemia, chronic bronchitis, and subacute bacterial endocarditis were present each in 1 case.

During this period in the New York Hospital there have been 114 inguinal hernias repaired to each femoral hernia.

Infection in the wounds in three patients as a postoperative complication is recorded and 1 each had a hematoma, thrombophlebitis, cerebral embolism, and cystitis. In the patient who developed cystitis the bladder was opened accidentally at the time of operation.

There were no deaths after operation in the series of 113 patients.

In four patients the last visit was less than 6 months after operation, three of these died within 6 months of their discharge. Therefore, there are 115 operations upon patients who have been traced, seen, and examined 6 months to 8 years after operation. One hundred and six operations have been checked one year after they were performed. It is generally agreed that 90 per cent of hernias which recur do so within the first year after operation save when a recurrent hernia is repaired or when the wound becomes infected. In this series all recurrences were noted within a year save two, one of which had been repaired previously and one in which a wound infection developed.

In the method of repair, there have been minor variations. All operations have been divided into two groups: in the first the approach was made below Poupart's ligament (40 cases), and in the second the approach was above this structure (81 cases).

There were 8 recurrences in the 121 hernias and each of these had been repaired from above Poupart's ligament, a recurrence rate of 6.6 per cent for all cases and 10 per cent for those repaired by the inguinal route. A summary of the histories of the patients with recurrences of hernia following operation is presented later.

#### RECURRENTS

1 (Case 10) — A 52 year old man had a right femoral hernia which was repaired with silk under local anesthesia. The approach was from above Poupart's ligament. After operation his convalescence was uneventful. Within one year the hernia had recurred but the patient refused another operation.

2 (Case 16) — A 54 year old woman had a right incarcerated femoral hernia repaired with silk and under local anesthesia, the approach being above Poupart's ligament. The patient was obese and had diabetes. Her postoperative convalescence was uneventful but the hernia recurred in six months.

3 (Case 20) — A 29 year old woman had a right femoral hernia repaired with silk and under local anesthesia, from above Poupart's ligament. Convalescence was normal but within 6 months this hernia recurred. After another operation she had remained well for 3 years. At the time of the first operation she was 4 months pregnant and was subsequently delivered of a normal child.

4 (Case 62).—A 34-year-old white woman had a right femoral hernia repaired with silk through an inguinal approach under local anesthesia. Despite a normal recovery after operation, this hernia recurred in 8 months. The hernia was again repaired and the patient has remained well for 1 year.

5 (Case 67).—A 55-year-old white woman was admitted with bilateral femoral hernia. Ten years previously, at another hospital, the left side had been repaired but the hernia recurred within 6 months. Under ethylene anesthesia a bilateral repair was carried out with catgut as suture material. On the left side, although approached from above Poupart's ligament, it was necessary to divide this structure in order to reduce the hernia. After 5 years there is a recurrence on this side.

6 (Case 80).—A 48-year-old white man, with a right femoral hernia repaired with silk under local anesthesia, developed an infection of his wound. Again an inguinal approach had been used. Three years later this hernia recurred.

7 (Case 90).—In a 51-year-old male a right femoral hernia was repaired with silk under local anesthesia; it was approached from above Poupart's ligament. Convalescence was uneventful but the hernia recurred within 10 months. After another operation he has remained cured for 2 years.

8 (Case 116).—A 32-year-old white woman with a right femoral hernia had been operated upon in another hospital, 1 year previously, for an inguinal hernia which was not found. Repair with silk under local anesthesia and inguinal approach were followed by a smooth convalescence but a recurrence was noted 2 months later. This patient was again operated upon 2 months ago and remains well to date.

In the repair of a femoral hernia no single type of operation can be used for every case. A strangulated femoral hernia, for instance, should be approached from above Poupart's ligament so that an intestinal resection can be carried out if necessary. The method here described approaches the hernia from below Poupart's ligament but the repair is carried out as advocated by those who use the inguinal approach. Poupart's is sutured to Cooper's ligament, closing the femoral canal at its internal opening without the additional strain of a repair of the floor of the inguinal canal and also without the incision of the transversalis fascia.

#### SUMMARY AND CONCLUSIONS

1. A procedure which combines the better features of the two standard operations for the repair of a femoral hernia is presented.

2. The usual operations for femoral hernia are described and discussed.

3. The experiences with the surgical treatment of femoral hernia at the New York Hospital are reviewed with particular emphasis on late results and recurrences.

4. No single type of operation or approach can be used advantageously for the repair of every femoral hernia. The rate of recurrence is higher in those cases which are approached from above Poupart's ligament. Cooper's ligament may be sutured to Poupart's as effectively from below as from above Poupart's ligament.

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dilated, and the respirations decreased to 14. He became difficult to arouse. A provisional diagnosis was made of slow hemorrhage from the left middle meningeal artery and the operating room prepared for exploratory trephine. Meanwhile, x-ray of the skull showed a horizontal transverse fracture across the entire frontal bone just above the sinus level. Before operation at 9:30 P.M. the respirations had receded to 12 and the temperature was 103° F. The pulse pressure was 50. I exposed the left middle meningeal artery and found it to be intact but quite large. There was no evidence of bleeding from the anterior or posterior branch. The dura, however, was tense and bulged and upon its incision there was a copious gush of clear subdural fluid. The brain was gently retracted and at least 2 oz. (60 c.c.) of the fluid quickly ran out. Within ten minutes the patient awakened on the table and responded to questioning. A drain was placed in the subdural space and the dressings were very wet for thirty-six hours, when they were changed and the drain removed. Twelve hours after the operation there was practically complete return of function of the right side and the pupils had receded to normal size. The temperature fell by lysis in three days and the patient was discharged on the tenth day postoperatively with no complaints, talking well, and with no residual paralysis. A follow up two years later showed a bright healthy child with no recurrence of attacks since the operation.

## COMMENTS

This case illustrates that the typical symptoms and signs of epidural hemorrhage can be simulated by an acute collection of clear subdural fluid. It shows the harmful effects from the use of morphine sulfate or its derivatives in the treatment of status epilepticus, and the emergency value of intranasal carbon dioxide and oxygen, coramine, spinal drainage and dehydration in acute cerebral compression, and, finally, the therapeutic value of draining the subdural space. The large amount of clear subdural fluid removed was taking up as much space and exerting as much pressure against the brain as would an equivalent volume of epidural or subdural liquid blood or clot.

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## ACUTE SUBDURAL HYDROMA SIMULATING SYNDROME OF EXTRADURAL HEMORRHAGE

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ALTHOUGH the classical signs and treatment for acute epidural hemorrhage are well known, it is not generally recognized that following head trauma an acute unilateral collection of clear fluid in the subdural space may give rise to similar symptoms and demand prompt operative drainage of the subdural space. Naffziger,<sup>1</sup> Cohen,<sup>2</sup> Dandy,<sup>3</sup> Love,<sup>4</sup> Walsh and Sheldon<sup>5</sup> and others have called attention to collections of clear fluid in the subdural space following head trauma resulting in symptoms of cerebral compression often simulating subdural hematoma. This accumulation of fluid may result in acute or chronic symptoms, and since it cannot be removed by spinal drainage, an opening in the dura is necessary. It is believed that the fluid enters the subdural space through a rent in the arachnoid and becomes trapped.

Case 1 illustrates how an acute collection of this clear fluid in the subdural space can simulate the classical symptoms and signs of middle meningeal extradural hemorrhage.

CASE 1.—P. S., aged 9 years, was admitted to the neurosurgical service on May 7, 1939, with a history of head injury followed by right-sided jacksonian convulsions, right hemiparesis, and cyanosis. There was no history of previous attacks. At 2:30 P.M., one hour after the injury, twitching began of the right side of the face and the right hand, the patient became unconscious, the entire right side of the body convulsed, and the child became very cyanotic. A physician found the boy in right-sided status epilepticus, very cyanotic, and noticed that the left pupil was markedly dilated. He gave pantopon, gr.  $\frac{1}{6}$ , hypodermically and in fifteen minutes the attack stopped but the patient became more cyanotic and the respirations decreased to eight per minute. The boy was admitted to the hospital and examined at 5:30 P.M. He was in deep stupor. The pupils were now constricted and equal in size. The respirations were 6 and sighing in type. The pulse was difficult to feel. Carbon dioxide in oxygen, 10 per cent, was given intranasally and 3 gr. of coramine were given subcutaneously. Lumbar puncture showed a pressure of 12 mm. of mercury with slightly pink spinal fluid. Because an epidural hemorrhage was suspected only 4 c.c. were very slowly removed, leaving a final pressure of 8 mm. of mercury. In fifteen minutes the respirations rose to 12, he reacted to painful stimuli, and it was noticed that a right hemiparesis with Babinski sign was present. The patient was then given a hypertonic magnesium sulfate enema (magnesium sulfate crystals, 3 oz.; glycerin, 1 oz.; and water, 12 oz.). By 7:30 P.M. (six hours after the injury) the respirations were up to 16, the boy opened his eyes, talked, and moved the right side slightly. The left pupil was only slightly larger than the right. At 8:00 P.M. the patient became drowsy again, the left pupil

dilated, and the respirations decreased to 14. He became difficult to arouse. A provisional diagnosis was made of slow hemorrhage from the left middle meningeal artery and the operating room prepared for exploratory trephine. Meanwhile, x-ray of the skull showed a horizontal transverse fracture across the entire frontal bone just above the sinus level. Before operation at 9:30 P.M. the respirations had receded to 12 and the temperature was 103° F. The pulse pressure was 50. I exposed the left middle meningeal artery and found it to be intact but quite large. There was no evidence of bleeding from the anterior or posterior branch. The dura, however, was tense and bulged and upon its incision there was a copious gush of clear subdural fluid. The brain was gently retracted and at least 2 oz. (60 c.c.) of the fluid quickly ran out. Within ten minutes the patient awakened on the table and responded to questioning. A drain was placed in the subdural space and the dressings were very wet for thirty-six hours, when they were changed and the drain removed. Twelve hours after the operation there was practically complete return of function of the right side and the pupils had receded to normal size. The temperature fell by lysis in three days and the patient was discharged on the tenth day postoperatively with no complaints, talking well, and with no residual paralysis. A follow-up two years later showed a bright healthy child with no recurrence of attacks since the operation.

## COMMENTS

This case illustrates that the typical symptoms and signs of epidural hemorrhage can be simulated by an acute collection of clear subdural fluid. It shows the harmful effects from the use of morphine sulfate or its derivatives in the treatment of status epilepticus, and the emergency value of intranasal carbon dioxide and oxygen, coramine, spinal drainage and dehydration in acute cerebral compression, and, finally, the therapeutic value of draining the subdural space. The large amount of clear subdural fluid removed was taking up as much space and exerting as much pressure against the brain as would an equivalent volume of epidural or subdural liquid blood or clot.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## THE THYMUS IN MYASTHENIA GRAVIS

WITH OBSERVATIONS ON THE NORMAL ANATOMY AND HISTOLOGY OF THE THYMUS

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BLALOCK, Harvey, Ford, and Lilienthal<sup>1</sup> have reported the effects of removing the thymus from six patients with myasthenia gravis; more recently Blalock has removed the thymus from four additional patients. The diagnosis in each case was confirmed by the response to prostigmine salts and the intra-arterial injection of prostigmine methyl-sulfate. Stimulated by the marked improvement in some of these cases following operation, an investigation of the pathology of the thymus in myasthenia gravis was begun. None of the ten operative specimens examined contained a tumor. In order to establish a basis for comparison 350 thymus glands were examined between August 5, 1941, and March 23, 1942. These included approximately 200 specimens removed during routine autopsies at the Johns Hopkins Hospital and 150 specimens removed from patients who died suddenly and were autopsied at the city morgue.†

### EMBRYOLOGY AND HISTOLOGY

It is usually stated that during the sixth week of embryonic life the thymus arises as ventral, cylindrical outgrowths of the third pair of pharyngeal pouches. These hollow epithelial cylinders, arising from the entoderm, soon elongate, become solid, and enlarge at their free ends. Simultaneously, parathyroid III arises from the dorsal diverticulum of the third pharyngeal pouch. During this process the mesial portions of the pharyngeal pouches, lying between these structures and the pharynx, atrophy and disappear. Thus, the two lobes of the thymus, accompanied by the detached cervical sinus, and the two parathyroids become independent structures. The caudal end of the thymus enlarges. With the great vessels and the heart, the thymus and parathyroid III move caudally towards the thorax. Parathyroid III normally ceases its descent near the lower pole of the thyroid, the thymus separating from it as it progresses into the thorax. The two lobes extend over

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†Dr. W. G. VandeGrift, assistant medical examiner, made it possible for these specimens to be obtained.

the innominate vein and upper portion of the pericardium where they form the body of the gland, although they never actually fuse. After the second month of embryonic life the solid epithelial cords are transformed into a loose network of epithelial cells. These proliferate to form rounded masses which are the lobules. The lobules are never entirely separated from one another since they represent projections from a central core of thymic tissue. There is an ingrowth of blood vessels. Connective tissue from the adventitia of these blood vessels and from the capsule of the gland forms a stroma. With the appearance of blood vessels in the thymus the interstices of the network of epithelial cells become filled with the small thymic cells and the lobules are definitely divided into a cortex and medulla.<sup>2-4</sup>

The origin of the small thymic cells is uncertain but they are probably identical with lymphocytes. The epithelial cells in the thymus are derived from the entoderm of the third pharyngeal pouch. During the process of differentiation of the thymus into cortex and medulla, concentric masses of cells appear in the sheets of epithelial cells of the medulla. These are the Hassall corpuscles and are commonly believed to be derived from the epithelium of the medulla.<sup>4-6</sup> Norris,<sup>7</sup> however, has recently stated that the thymus has both an entodermal component derived from the third pharyngeal pouch and an ectodermal component derived from the third branchial cleft through the cervical sinus. He believes the Hassall corpuscles are derived from the ectodermal elements and not from the epithelium of the medulla, which is of entodermal origin. This view has not yet been widely accepted.

In the normal infant, at birth, the lobules of the thymus are sharply divided into a cortex and medulla. The cortex consists of closely packed masses of lymphocytes. Scattered among these lymphocytes there are a few large cells with ovoid, pale-staining nuclei, and moderate amounts of poorly outlined cytoplasm. These are indistinguishable from the similar but more numerous epithelial cells of the medulla. Occasional blood vessels are seen in the cortex. Little connective tissue stroma seems to be present.

There is a loose stroma of connective tissue in the medulla. Many epithelial cells are present and in some areas they form irregular sheets in which the individual cell outline is lost. At varying intervals in them there are the concentric masses which are Hassall corpuscles. The Hassall corpuscles undergo hyaline necrosis and often calcification. Their number, age, and size vary greatly with the individual gland. Lymphocytes are scattered through the medulla but are present in much smaller numbers than in the cortex. Other types of cells, chiefly eosinophiles, are often found in the medulla. The blood supply of each lobule passes through the medulla into the cortex, and vessels of considerable size are present in the medulla.

In the debate about the origin of the small thymic cells and the relation of the thymus to the lymphatic structures of the body, it has been

stated that the human thymus does not contain lymphoid follicles.<sup>8-11</sup> Lymphoid follicles with germinal centers have been described in the thymus of the cat.<sup>12</sup> They have also been described in the human thymus in hyperthyroidism<sup>13</sup> and myasthenia gravis.<sup>14, 15</sup> As will be shown, the presence of lymphoid follicles with germinal centers is a prominent aspect of the changes seen in several of the thymus glands examined from patients with myasthenia gravis (Fig. 10).

The presence of lymphoid follicles with germinal centers in these glands led to a careful search of normal thymus glands for such follicles. Surprisingly enough they were found in the medulla of 14 of 150 glands from people who died suddenly without previous chronic disease. The lymphoid follicles had a typical configuration with a central area of irregular, large, pale cells grouped about a small blood vessel and surrounded by a ring of small lymphocytes. Large lymphocytes were scattered through the follicles and occasional mitotic figures could be seen. The cells forming the germinal centers differed markedly from the epithelial cells of the medulla, and the follicles did not have the stroma found elsewhere in the medulla. The lymphoid follicles were not found in the cortex.

When present in normal thymus glands the lymphoid follicles were found only in small numbers. Occasional lymphoid follicles might possibly be found in most normal glands if serial sections were cut. In this series of 350 cases they were not present in markedly involuted glands, or in those of the fourteen normal infants under 3 years of age examined.

#### ANATOMY

In the removal and dissection of the 350 thymus glands examined, the gross anatomy was studied and, except for minor details, was found to be that given in standard textbooks of anatomy.<sup>16, 17</sup> The thymus in the adult is a roughly triangular gland lying beneath the sternum in the anterior mediastinum and often extending into the neck. It consists usually of two lobes which may vary greatly in size or may be further subdivided. The lobes of the thymus in the normal adult are reddish yellow in color and are firmer than the surrounding yellow mediastinal fat in which they lie and from which they can be dissected easily.

Cervical extensions of the lobes of the thymus are present in the majority of cases. These extend into the neck and may reach the base of the thyroid gland. They may be partially or almost completely separated from the thoracic portions of the gland. Often only one cervical extension is present, the other lobe being entirely intrathoracic. They are frequently connected to the base of the thyroid by thin strands of fibrous tissue, the so-called thyrothymic ligament, in which tiny blood vessels run.

The thymus is separated from the sternum by a thin but definite film of loose connective tissue which must be incised to expose the gland.

Through this run small blood vessels connecting the structures in the anterior mediastinum with the internal mammary vessels. Overlying the thymus partially on each side are the pleural reflections which must be dissected laterally in order to expose the gland adequately. The thymus may extend inferiorly over the pericardium to the third, fourth, or fifth ribs. It may extend laterally to the phrenic nerve and hilum of the lung, although this is rare in the adult. The gland lies on the pericardium and great vessels to which it is attached by strands of connective tissue, apparently a continuation of the pretracheal division of the deep cervical fascia in the mediastinum. This connective tissue also attaches the lobes to one another. The thymus is in especially close contact with the left innominate vein and it may partially surround this vessel. In the neck the cervical extensions lie beneath the pretracheal division of the deep cervical fascia and the sternothyroid muscles. They overlie the trachea and large vessels in the neck (Fig. 1).

Abnormalities in the position and shape of the thymus are not uncommon.<sup>18</sup> Complete absence of the gland in the infant has been reported.<sup>19</sup> Occasionally one lobe may be quite small or may lie entirely within the neck. The cervical extensions may reach superiorly beyond the thyroid. Thymic tissue has been described far laterally in the neck.<sup>20</sup> Tiny aberrant nodules of thymic tissue in the neck have been reported as occurring rather frequently in children.<sup>21</sup> The position of these nodules may vary greatly. Usually they are found about or within the thyroid. They have been reported in the larynx<sup>22</sup> and in the ear.<sup>23</sup> The gland may lie beneath the innominate vein and one case has been seen in the present series of 350 cases in which the lobes crossed over each other, one anterior to the innominate vein, and one posterior to it.

In the specimens examined, no aberrant nodules of thymic tissue were found. However, it was impossible to expose the neck region adequately and such nodules, even if present, might easily have been missed.

The arterial supply of the thymus (Fig. 2) is derived from three chief sources: the internal mammary arteries, the inferior thyroid arteries, and the pericardiophrenic arteries. The principal portion of this arterial supply arises from the internal mammary artery near the sternoclavicular joint. In addition to observations made on autopsy specimens and at operation, two dissections in cadavers have confirmed this. A branch supplying the thymus has also been found arising from the transverse scapular artery.\*

The venous return from the thymus passes into a network of veins on the posterior surface of the thymus, between the thymus and the pericardium. Here a single large vein draining each lobe is formed. This may empty directly into the left innominate vein or may join the vein from the other lobe to form a single large vessel emptying into the left innominate vein. The inferior thyroid veins and the thyroidea ima

\*The dissections were carried out by Miss Browning, the medical artist responsible for the illustrations.

usually receive branches from the cervical portions of the thymus. Small veins may empty into the internal mammary veins and a branch has been found emptying into the left superior intercostal vein in one dissection.

The lymphatic drainage of the thymus has been the source of some controversy. The lymph channels are commonly said to drain into the

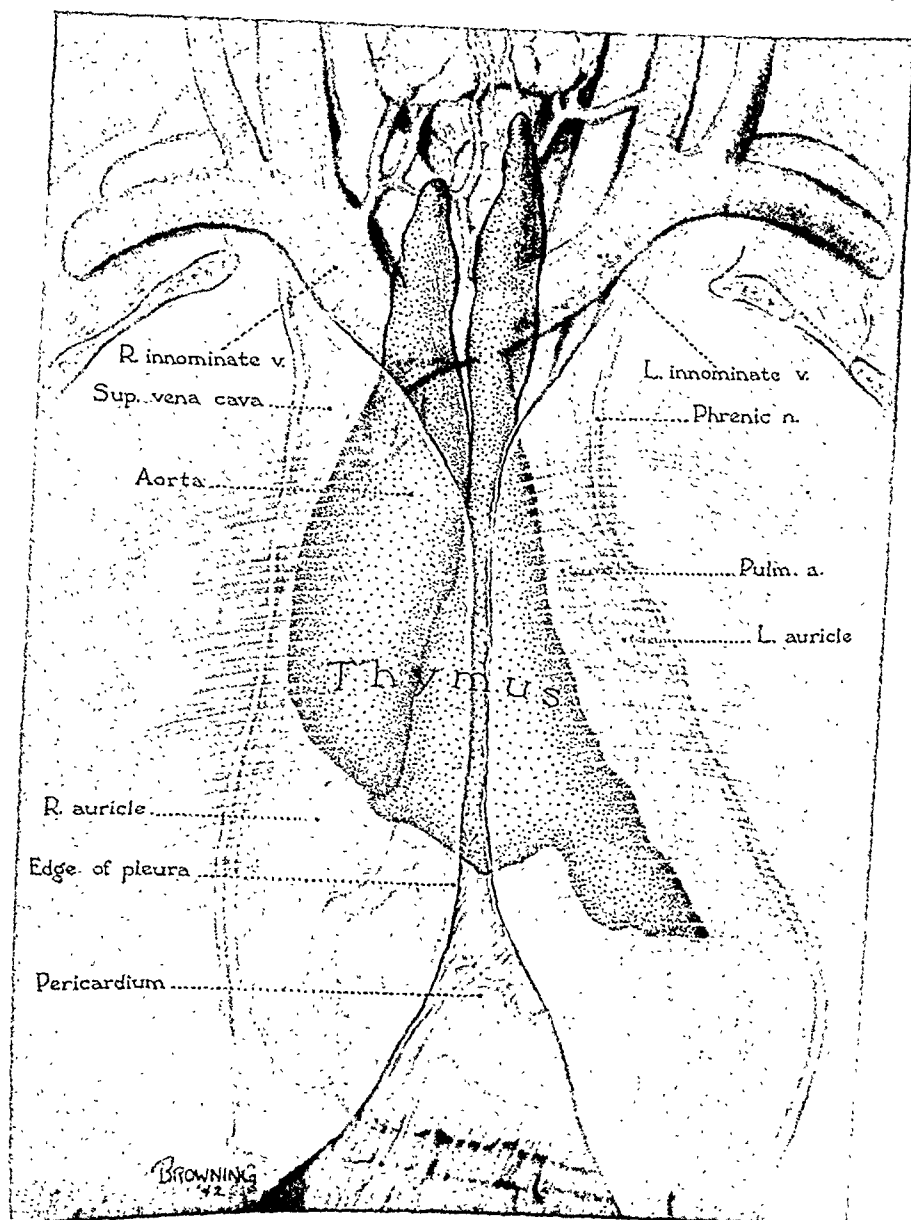


Fig. 1.—Relation of the thymus to the mediastinal structures.



superficial and deep cervical lymph nodes and lymph nodes in the mediastinum.<sup>24</sup> It has been stated, however, that there is a closed lymphatic system between the thyroid and the thymus, the thymus serving as a reservoir for thyroid secretions.<sup>25</sup> There is little to substantiate this viewpoint.<sup>24</sup>

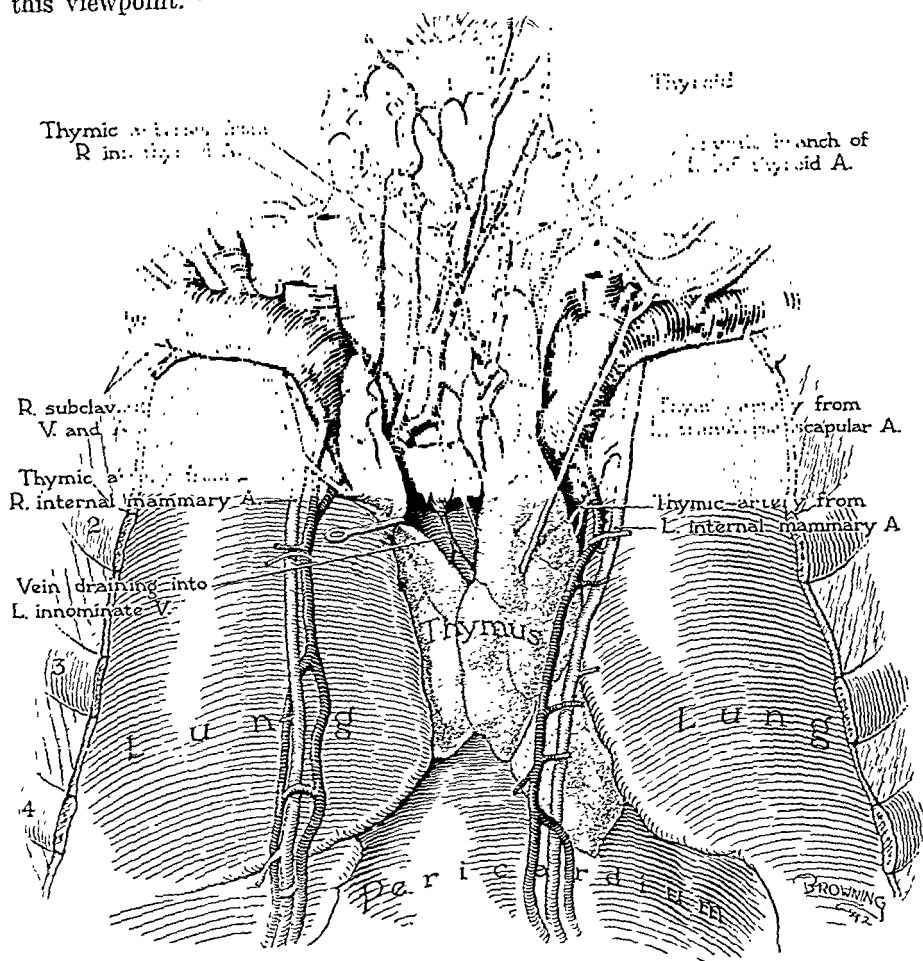


Fig. 2.—Vascular supply of the thymus.

The innervation of the thymus is similar to that of the thyroid and parathyroid glands. It arises from the cervical sympathetic chain and the vagus.<sup>26</sup> The nerve endings are traceable chiefly to the walls of the blood vessels.

#### INVOLUTION OF THE THYMUS (STUDY OF 350 CASES)

In examining the 350 thymus glands available for study from individuals dying suddenly and those dying after various illnesses, the well-known facts about the involution of the thymus were easily confirmed.<sup>27-29</sup> Attempts to employ the former group as a standard of

normal served to emphasize certain facts which have not been understood by previous writers describing the thymus in patients with myasthenia gravis.

In the child the thymus is a thick, solid, pinkish-gray gland which fills the anterior mediastinum. At about the age of puberty the gland undergoes marked changes. It becomes longer and more narrow as it comes to occupy a relatively smaller portion of the anterior mediastinum, although it actually may be larger than in childhood. The gland undergoes involution; that is, much of the thymic tissue present is replaced by adipose tissue lying between and widely separating the individual lobules from each other, and simultaneously the number of lymphocytes



Fig. 3.—Normal thymus of a child (11-year-old colored girl). The cortex and medulla are sharply differentiated; there is no age involution and the lobules are not separated by adipose tissue (magnification  $\times 20$ ).

in the cortex and medulla diminishes. However, with rare exceptions thymic tissue can be found in any person, whatever his age, duration of illness, or cause of death. The thymus can still be recognized as two masses of fatty tissue which preserve the outlines of the lobes of the thymus and which can be dissected easily from the surrounding mediastinal fat. This tissue will contain small amounts of thymic tissue which can be identified easily on microscopic examination. If the patient is emaciated and has lost most of the body fat, the thymus will be present as two thin, translucent tongues of grayish tissue overlying the pericardium.

Histologically in the child the gland consists almost entirely of thymic tissue (Fig. 3). The cortex, filled with closely packed lymphocytes, surrounds and overshadows the medulla, from which it is sharply demarcated. The well-formed lobules are separated only by thin strands of connective tissue. There is no adipose tissue between the lobules.

At about the age of puberty the gland begins to undergo a process known as age involution. This atrophy or age involution consists, as mentioned above, of a decrease in the amount of thymic tissue present in each lobule and the separation of the lobules from one another by masses of adipose tissue. In the involuting thymus the lymphocytes first decrease in number and later there is a reduction in the number of epithelial cells present. It should be emphasized that in this process, although the relative amount of cortex decreases considerably, the differentiation of cortex and medulla remains distinct until the gland is so greatly involuted that only a few small, widely separated islands of thymic tissue remain in which there can be seen epithelial cells, scattered lymphocytes, and rare hyaline or calcified Hassall corpuscles (Figs. 4 and 5).

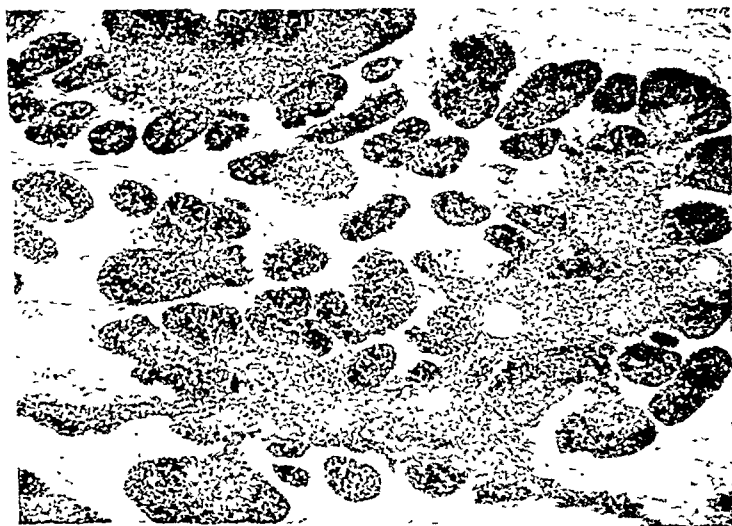


Fig. 4.—Normal thymus of an adult (a white male, 37 years of age); there is moderate age involution. The cortex and medulla are sharply demarcated (magnification  $\times 20$ ).

At any point in this process of age involution there may be an acceleration called accidental involution, brought on by illness<sup>27</sup> (Fig. 6). In a few days, even in infants, the lymphocytes may be markedly decreased in number, leaving chiefly the stroma and irregular sheets of epithelial cells. There is no evidence of continued growth of adipose tissue between the lobules during this accidentally accelerated involution, and the adipose tissue may atrophy and actually decrease in amount.<sup>29</sup>

The most interesting observations were made in patients meeting accidental death in the same age group as the patients in this series with myasthenia gravis, i.e., 20 to 45 years. Roughly the weights of these glands paralleled those recorded by Hammar.<sup>30</sup> However, just as in his cases, the extremes of weight were great, so great in fact that an average weight for a given age group was meaningless. Any gland could be

considered abnormal only if it exceeded the maximum weight recorded in the series. In addition, for any given age the thymus glands removed from normal individuals showed greatly varying degrees of involution. Some had undergone marked involution, consisting largely of fatty tissue and containing small lobules of thymic tissue. The thymic tissue present, however, showed a sharply distinguishable cortex and medulla. In



Fig 5.—Normal thymus (magnification  $\times 20$ ) of an adult (39-year-old white woman). Although from an individual of approximately the same age as that in Fig 4, there is a much greater degree of age involution



Fig. 6.—Thymus of a young adult (colored female, 19 years old) who died after a chronic illness, there is marked accidental involution. The epithelium is prominent and is as great in amount as that in the thymus glands of patients with myasthenia gravis (magnification  $\times 20$ ).

others there was little involution. The amount of fat present was small and the gland was made up of large lobules of thymic tissue in which the cortex and medulla were clearly demarcated, the cortex being relatively smaller in relation to the medulla than in the child (Figs. 4 and 5). This great variation in the amount of thymic and adipose tissue present in glands from normal individuals of the same age is clearly demonstrated in Hammar's diagrams.<sup>30</sup> Thus, several factors served to make meaningless any figures arrived at as the average normal weight of the thymus in an effort to establish significant standards by which to judge the size of the thymus glands removed from patients with myasthenia gravis. One was the great variation in the total weights of normal thymus glands. The others were the variations in the actual amounts of thymic tissue and of adipose tissue present even in glands of similar weight.

#### THE THYMUS IN TEN CASES OF MYASTHENIA GRAVIS

It has long been known that in certain diseases, notably hyperthyroidism, Addison's disease, acromegaly, and myasthenia gravis, the thymus may not atrophy, as in many illnesses, and that it may show certain rather characteristic changes. In some examples of myasthenia gravis the pathologic lesions found at autopsy may not be marked and may be limited to changes in the thymus. Norris<sup>31</sup> stated that 50 per cent of the cases of myasthenia gravis showed gross lesions of the thymus, and he believed that such lesions would be found in direct proportion to the care with which they were sought. In a series of fifty-four cases collected by Blalock and his associates<sup>32</sup> in which lesions of the thymus were present, these including all reported cases and one of their own, thirty-two showed tumors and twenty-two showed what was listed as persistence of hyperplasia. Lievre<sup>33</sup> recorded sixty-seven patients with myasthenia gravis in whom complete autopsies were performed. In twenty-four of these there was a mediastinal tumor in the region of the thymus. In thirty-two there was what was called persistence or hypertrophy of the thymus. In eleven no lesions were found. Of the five cases of myasthenia gravis autopsied at the Johns Hopkins Hospital and reported by Miller,<sup>14</sup> two showed tumors of the thymus, two were reported as being hyperplastic, and in one no recognizable thymic tissue was found at autopsy. In a recent case autopsied at this hospital there was a malignant tumor of the thymus with metastases to the left pleural surfaces. Of the eight cases of myasthenia gravis autopsied at the Mayo Clinic<sup>34</sup> one showed what was called nodular hyperplasia and the other a malignant thymic tumor with metastatic implantations on the pleura. No lesions were found in six cases. The total number of autopsied cases of myasthenia gravis reported up to the present time, including eight autopsied at the Mayo Clinic, is now stated to be ninety-nine, and in 45 per cent of these, anatomic lesions of the thymus have been found.<sup>35</sup>

Many of the thymus glands recorded in the literature as pathologic are listed as persistent, enlarged, or hyperplastic glands. It has been demonstrated that mere persistence of the thymus is not pathologic. The weights recorded in many of the so-called enlarged glands lie well within normal variations of weight for the thymus. Of the twenty-two glands listed in Blalock's series<sup>32</sup> as showing persistence or hyperplasia, the weight is recorded in ten. In only four is the weight in excess of normal and one of these cases, that of Mott and Barrada,<sup>36</sup> is probably a thymic tumor. The thymus glands reported as being hyperplastic have been described as showing lymphoid or epithelial hyperplasia without any detailed description of the changes present. Most attention has been centered on the tumors of the thymus in myasthenia gravis.

The material to be presented here provided an opportunity to examine ten thymus glands in which no tumor was present and to compare them with thymus glands of individuals in the same age group meeting sudden or accidental death. The clinical aspects of six of these cases have been reported by Blalock and his co-workers.<sup>1</sup> In the six cases when the glands were removed at operation, representative blocks were taken and the remainder quickly frozen for later extraction. For this reason the gross descriptions of these thymus glands are somewhat meager. Only one of the glands was weighed and no measurements were taken in two cases. At a later date the portions of the glands which had been frozen were thoroughly sectioned to ascertain the presence of small tumors which might have been missed previously. At this time further blocks were taken for microscopic examination. The thymus glands in the four additional cases were accurately weighed and measured, none being taken for extraction.

#### REPORT OF CASES

CASE 1.—P. C., a 33-year-old colored male, had an eight months' history of increasingly severe weakness, requiring before operation a total daily oral dose of 240 mg. of prostigmine bromide before he could get out of bed and feed himself. There was no clinically recognizable lymphoid hyperplasia.

At operation the thymus was found to extend in the midline from the base of the thyroid to the fifth costal cartilage. Made up of well-formed, firm tissue, the gland could not be confused with fat. (The operator identified but a single lobe of the thymus and the possibility remains that the patient retains his other lobe.) The tissue removed was not weighed or measured and no tumor was found.

Microscopically, the thymus showed evidence of involution, for the lobules of thymic tissue were separated by considerable amounts of fatty tissue. The cortex consisted of small masses of closely packed lymphocytes. It was poorly demarcated from the medulla because the medulla was diffusely infiltrated with many lymphocytes. In places the medulla contained rounded accumulations of lymphoid cells and in two areas were small groups of large, pale, irregular cells resembling those seen in germinal centers. These were not surrounded by the ring of small lymphocytes usually seen in lymphoid follicles. Considerable numbers of epithelial cells were present in the medulla. Despite the infiltration with lymphocytes, the epithelial cells in places formed irregular sheets. However, no evidence of epithelial hyperplasia was present. A moderate number of Hassall corpuscles was seen and most of these showed hyaline necrosis.

CASE 2.—R. L., a white woman, 28 years of age, had progressively severe weakness for a year. On admission she was taking 1 Gm. of guanidine and six or seven 30 mg. doses of prostigmine bromide each day. Still she was confined to bed. There was no clinical lymphoid hyperplasia.

At operation, a gland twice the size of that in Case 1 was found. It was formed of two lobes which began at the lower poles of the thyroid, extended downward as two separate lobes to the level of the third costal cartilage, and then formed a single mass which terminated at the level of the fifth costal cartilage. The thymic tissue was grossly firm and well formed. No measurements were taken. There was no tumor present.

On microscopic examination there was a moderate degree of involution, for the distinct lobules of the gland were separated from one another by adipose tissue. Again there was considerable amount of cortical tissue consisting of rather closely packed masses of lymphocytes. The cortex was greater in amount and the lymphocytes more closely packed than in thymus glands with a similar degree of involution in individuals of the same age. The differentiation between cortex and medulla was less sharp than normal. The medulla was diffusely infiltrated with lymphocytes and these tended to separate the epithelial cells so that they were scattered individually through the medulla and did not form the irregular sheets usually seen. There were no lymphoid follicles present in the medulla and there was no epithelial hyperplasia. The many large Hassall corpuscles showed hyaline necrosis.



Fig. 7.—Thymus of patient in Case 3 (22-year-old colored female). There is a great increase in the number of lymphocytes present, especially in the medulla; the demarcation between cortex and medulla is indistinct. Lymphoid follicles with germinal centers can be seen (magnification  $\times 20$ ).

CASE 3.—L. K., 22-year-old colored woman, had a six-year history, the disease being moderately severe for three and one-half years. On admission she required 105 to 120 mg. of prostigmine bromide a day but remained severely handicapped by her illness. There was no clinical evidence of lymphoid hyperplasia.

Operation disclosed a large, firm thymus with well-defined right and left lobes. These extended from the lower poles of the thyroid to the level of the third interspace and in their thoracic positions spread rather far laterally. The right lobe measured 9 by 2.5 by 0.8 cm., and the left lobe 15 by 2.5 by 0.8 cm. No tumor was found.

Involution in this gland (Fig. 7) was slight and it consisted almost entirely of thymic tissue. Areas of cortex were seen but these were so poorly demarcated from the medulla, which was densely infiltrated with lymphocytes, that each lobule presented an almost homogeneous appearance. In the medulla there were numerous large, lymphoid follicles with prominent germinal centers. In many of these, mitotic figures were present. The epithelial cells in the medulla were widely separated and almost obscured by the many lymphocytes. There was no evidence of epithelial hyperplasia. Few Hassall corpuscles were present in the gland.

The lack of involution in this thymus was not unusual, for occasional glands in normal individuals of the same age showed as little involution as was present here. However, in such normal thymuses the cortex and medulla were sharply demarcated and each contained fewer lymphocytes.

CASE 4.—H. M., a woman 39 years of age, had a five and one-half-year history of mild myasthenia gravis, weakness being limited largely to those muscles innervated by the cranial nerves. The patient died following operation.

Operation showed a moderate amount of thymic tissue above the innominate veins, although the majority of the gland lay over the pericardium. The two large lobes extended from the midline rather far to either side, the left lobe reaching the hilum of the left lung. The right lobe measured 9 by 3 by 0.8 cm., the left lobe 15.5 by 2 by 0.5 cm. There was no tumor present.



Fig. 8.—Thymus of Case 4 (a white woman, 39 years of age). Although there is marked age involution, the increase in the size of the lobules due to the increased number of lymphocytes present is easily seen (magnification  $\times 20$ ).

Sections of this gland (Fig. 8) differed in some respects rather markedly from those already described. Involution was far advanced, for the thymus contained large amounts of adipose tissue and only small scattered lobules of thymic tissue, but these lobules were much larger than in normal glands showing a similar degree of involution. No differentiation between cortex and medulla was visible. Instead, there was diffuse infiltration of each lobule of tissue with lymphocytes which could be seen spreading into the fatty tissue about the remnants of the thymus. Several lymphoid follicles with germinal centers were present. The epithelium was overshadowed by the lymphoid cells and only small amounts were seen. Rare, small Hassall corpuscles were found.



In normal glands at this stage of involution few lymphocytes were present and the small lobules consisted almost entirely of epithelial cells and stroma.

Autopsy was limited to the thorax and none of the endocrine glands were obtained for examination. The thymus had been completely removed at operation. There was no lymphoid hyperplasia present in the thorax.

CASE 5.—R. S., a 30-year-old white woman, had for seven months moderately progressive weakness until before operation she required 120 mg. of prostigmine bromide each day. There was no clinical lymphoid hyperplasia.

Most of the thymic tissue found at operation lay inferior to the innominate vein but there was a horn extending up on the left side to the inferior pole of the thyroid. At the upper part of the heart the lobes were broad and extended far laterally. The thymic tissue was firm. The right lobe of the thymus measured 8 by 2.5 by 0.8 cm., the left lobe measured 8 by 2.5 by 0.8 cm., while its cervical projection measured 9 by 6.1 by 0.8 cm. The gland weighed 30 gm. There was no tumor.

Microscopic examination of this gland showed considerable involution, for the lobules of thymic tissue were rather widely separated by fatty tissue. The changes in this thymus were less marked than in any other of the series. The cortex and medulla were rather sharply differentiated. Epithelial cells were easily distinguishable in the medulla and numerous Hassall corpuscles showing varying degrees of hyaline necrosis were present. There was no epithelial hyperplasia; however, the cortex showed a greater number of more closely packed lymphocytes than normal. There were abnormal numbers of lymphocytes in the medulla, and in places they formed small rounded accumulations. No lymphoid follicles with germinal centers were found.

CASE 6.—M. W., a white woman, 34 years of age, had a two-year history of progressive weakness of moderate severity. On admission, 15 mg. of prostigmine bromide every two hours both day and night did not permit her to walk by herself. There was no clinical lymphoid hyperplasia.

At operation the bilobed thymus extended from the thyroid gland to the fourth costal cartilage or slightly lower. Each lobe measured approximately 12 by 2.5 by 0.8 cm. There was no tumor.

The picture seen on microscopic examination of this thymus was like that seen in several of the other glands. There was a moderate degree of involution. The cortex was densely packed with lymphocytes and was more abundant than in normal glands showing a similar degree of involution. The medulla was heavily infiltrated with lymphocytes and the demarcation between cortex and medulla was indistinct. Numerous large lymphoid follicles with germinal centers were present in the medulla. The epithelial cells were partially obscured by the many lymphocytes about them. There was no epithelial hyperplasia. Many Hassall corpuscles showing hyaline necrosis were present.

CASE 7.—L. G., a white woman, 23 years old, had a five-year history of progressive weakness with remissions during two pregnancies. During the eight months preceding operation the patient's symptoms were well controlled by 150 mg. of prostigmine each day. There was no clinical evidence of general lymphoid hyperplasia.

At operation a firm, bilobed thymus was found. The right lobe measured 16 by 3 by 0.8 cm., the left lobe 14.5 by 3 by 0.8 cm. The gland weighed 28 Gm. There were definite cervical extensions into the neck, the right lobe extending 1.5 cm. higher than the left. The thymus grossly showed evidence of involution but many pinkish-gray lobules of thymic tissue were visible on section. On careful examination there was no tumor to be found.

On microscopic examination the gland showed definite evidence of involution, for the lobules were separated by small amounts of adipose tissue. A recognizable cortex

Involution in this gland (Fig. 7) was slight and it consisted almost entirely of thymic tissue. Areas of cortex were seen but these were so poorly demarcated from the medulla, which was densely infiltrated with lymphocytes, that each lobule presented an almost homogeneous appearance. In the medulla there were numerous large, lymphoid follicles with prominent germinal centers. In many of these, mitotic figures were present. The epithelial cells in the medulla were widely separated and almost obscured by the many lymphocytes. There was no evidence of epithelial hyperplasia. Few Hassall corpuscles were present in the gland.

The lack of involution in this thymus was not unusual, for occasional glands in normal individuals of the same age showed as little involution as was present here. However, in such normal thymuses the cortex and medulla were sharply demarcated and each contained fewer lymphocytes.

CASE 4.—H. M., a woman 39 years of age, had a five and one-half-year history of mild myasthenia gravis, weakness being limited largely to those muscles innervated by the cranial nerves. The patient died following operation.

Operation showed a moderate amount of thymic tissue above the innominate veins, although the majority of the gland lay over the pericardium. The two large lobes extended from the midline rather far to either side, the left lobe reaching the hilum of the left lung. The right lobe measured 9 by 3 by 0.8 cm., the left lobe 15.5 by 2 by 0.5 cm. There was no tumor present.



Fig. 8.—Thymus of Case 4 (a white woman, 39 years of age). Although there is marked age involution, the increase in the size of the lobules due to the increased number of lymphocytes present is easily seen (magnification  $\times 20$ ).

Sections of this gland (Fig. 8) differed in some respects rather markedly from those already described. Involution was far advanced, for the thymus contained large amounts of adipose tissue and only small scattered lobules of thymic tissue, but these lobules were much larger than in normal glands showing a similar degree of involution. No differentiation between cortex and medulla was visible. Instead, there was diffuse infiltration of each lobule of tissue with lymphocytes which could be seen spreading into the fatty tissue about the remnants of the thymus. Several lymphoid follicles with germinal centers were present. The epithelium was overshadowed by the lymphoid cells and only small amounts were seen. Rare, small Hassall corpuscles were found.

tomy two years before admission. Following this the exophthalmos continued. A month after her thyroidectomy the patient had progressively increasing weakness until she remained a semi-invalid despite 45 mg. of prostigmine every four hours. There was no clinical lymphoid hyperplasia.

At operation a small, firm, well-demarcated, bilobed thymus was removed. The right lobe measured 12.5 by 3.5 by 1.0 cm., the left lobe 10.5 by 1.5 by 0.8 cm. The gland weighed 15 Gm. There was no tumor.

There was involution of the thymus on microscopic examination for the lobules were separated by adipose tissue (Fig. 9). Each lobule was larger than normal due to a marked increase in the number of lymphocytes present in both the cortex and medulla. The normal sharp demarcation between cortex and medulla was lost. In the medulla were large numbers of lymphoid follicles with prominent germinal centers. There were also in the medulla irregular sheets of large, pale cells with poorly outlined cytoplasm. These epithelial cells were present in considerable numbers but there were no more of them than can be found in many normal glands in patients of the same age group. There were moderate numbers of Hassall's corpuscles present. These varied considerably in size and most of them were hyaline.

CASE 10.—H. M., a white woman, 27 years of age, had a two-year history of progressively severe weakness. Six months after the onset of her illness she delivered a child in a normal labor. On admission the patient was taking 90 to 135 mg. of prostigmine each day. On this she did fairly well but each morning after a night without prostigmine she was unable to raise her arms. There was no clinical lymphoid hyperplasia.

At operation a well-formed thymus with two lobes extending from the inferior pole of the thyroid to the fourth interspace was found. The right lobe measured 13 by 3 by 0.8 cm., and the left lobe 15.5 by 2.2 by 0.7. The gland weighed 25 Gm. No tumor was present.

On microscopic examination the thymus showed definite involution for the lobules were separated by small amounts of adipose tissue. Each lobule was larger than normal and this increase in size was due to the presence of large numbers of lymphocytes in the cortex and medulla. The normal sharp differentiation between cortex and medulla was lost. In the medulla there were large numbers of lymphoid follicles with prominent germinal centers. The epithelial cells in the medulla formed small, irregular sheets. Only a few, tiny Hassall corpuscles were present. There was no epithelial hyperplasia.

#### DISCUSSION

In two of Miller's series<sup>14</sup> of five cases of myasthenia gravis no tumor was found and the thymus glands were said to show epithelial hyperplasia. These cases have been re-examined with the changes described in mind. One thymus in a 45-year-old white man with an eight-month history of progressive weakness weighed 60 Gm. and each lobe measured 7 by 3 by 1.5 cm. The picture presented was much like Case 4 of this series. The sections showed a considerable degree of involution, there being relatively little thymic tissue in a fatty gland. No definite distinction between the cortex and medulla was present and the tissue was uniformly infiltrated with lymphocytes. In the medulla were many large lymphoid follicles with prominent germinal centers. The amount of epithelium present was not in excess of normal and there was no evidence of epithelial hyperplasia. The Hassall corpuscles showed hyaline necrosis and calcification. No generalized lymphoid hyperplasia was found in the other organs.

and medulla were present but both were densely infiltrated with lymphocytes and the normal, sharp demarcation of cortex and medulla was absent. Numerous large lymphoid follicles with germinal centers were present in the medulla. In this thymus the epithelium of the medulla could be seen plainly as irregular sheets of cells but the epithelium was no more prominent than in the glands of many individuals without myasthenia. Only rare small Hassall corpuscles were present.

CASE 8.—M. C., a 37-year-old white woman, had a nine-year history of progressive weakness. For two years the patient had remained in bed, a helpless invalid, despite large amounts of prostigmine. No general glandular enlargement was present.

At operation a small thymus gland was found overlying the base of the heart and the great vessels. There were no cervical extensions. The gland was dissected free with some difficulty and was not as sharply demarcated from the surrounding mediastinal fat as in some of the other cases. The right lobe measured 10 by 1.5 by 0.7 cm., and the left lobe 9.5 by 1.5 by 0.7 cm. The gland weighed 13 Gm. The thymus was firm, large and yellow-red in color. On section, numerous large scattered lobules of thymic tissue were seen. No tumor was found.

On microscopic examination the thymus showed characteristic changes. There was moderate involution and the lobules of thymic tissue were separated by considerable amounts of adipose tissue. The individual lobules of thymic tissue were larger than those seen in normal glands showing a similar degree of involution. This increase in the size of the lobules of thymic tissue was due to an increase in the number of lymphocytes present in the cortex and medulla of each lobule. The normal sharp differentiation between the cortex and medulla was lost. In the medulla there were large numbers of lymphoid follicles with prominent germinal centers. Irregular sheets of epithelial cells were present but these were no more prominent than in the glands of many individuals without myasthenia. There were only a few small Hassall bodies.

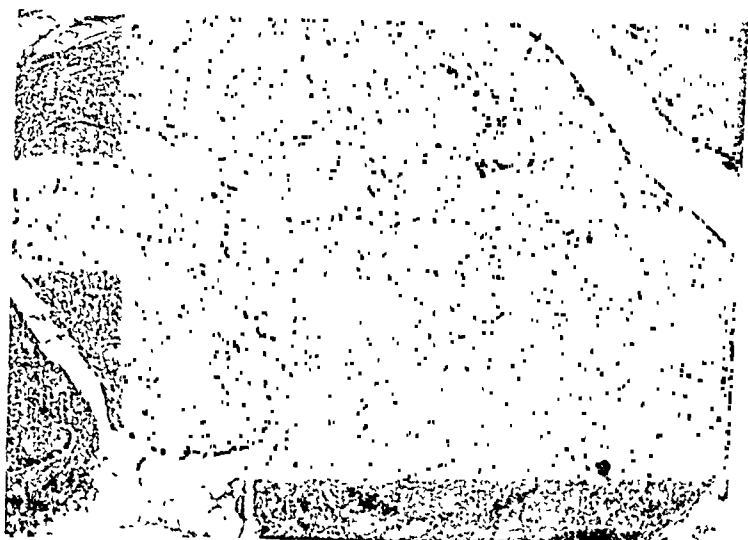


Fig. 9.—Thymus of Case 9 (a 24-year-old white woman). The increase in the size of the lobules and the large number of lymphoid follicles with germinal centers are clearly demonstrated (magnification  $\times 20$ ).

CASE 9.—M. W., a white woman, 24 years old, following the birth of her second child four years before admission, began to have increasing nervousness and definite exophthalmos. Basal metabolic rate was reported as plus 30 previous to a thyroidec-

of the cases this infiltration was accompanied by the presence in the medulla of abnormal numbers of lymphoid follicles with germinal centers (Fig. 10). None of the thymus glands showed evidence of epithelial hyperplasia. There were no constant changes in the character or number of the Hassall corpuscles.

It was considered possible that the changes observed in the thymus glands removed from patients with myasthenia gravis might represent part of a generalized lymphoid hyperplasia. Six autopsied cases of myasthenia gravis were examined. Five were those reported by Miller.<sup>14</sup> The sixth was a patient with myasthenia gravis in whom a tumor metastasizing to the left pleural cavity was found. In this case a tumor measuring 8 by 6.5 by 3 cm. was present in the anterior mediastinum in the position of the thymus. It contained both lymphoid and epithelial elements and was not different from the benign thymic tumors called thymomas. The numerous metastases on the left visceral and parietal pleuras were similar microscopically to the original tumor. There were no other metastases. Lymphorrhages were present in the muscles, but the other organs showed no lesions. No normal thymic tissue was found. In one case in which a benign tumor of the thymus was present there was slight enlargement of the mediastinal and cervical lymph nodes and the pharyngeal lymphoid tissue. In none of the others was there any evidence of generalized lymphoid hyperplasia.\*

It is unfortunate that more accurate gross descriptions of the thymus glands in this series were not available. The weights of five of the glands were 30, 28, 25, 15, and 13 Gm. These lie within the range of normal. Of those glands which were measured, none was larger than some normal glands in the same age group. However, the great variation in the amounts of thymic and adipose tissue actually present in the glands makes comparisons of weight valueless. Undoubtedly a few of the thymus glands found in cases of myasthenia gravis have weighed more than normal glands. Without knowing the relative amounts of thymic and adipose tissue present, it is impossible to say whether there was actually in these cases an increase in the amount of thymic tissue. The criteria of abnormality are not to be sought in the size of the gland but rather in its microscopic appearance.

Whether or not the thymus is enlarged in myasthenia gravis when compared with normal glands may be an academic point for still another reason. Patients suffering with this disease have been subjected to a long, often debilitating illness which may, through inability to swallow, produce considerable loss of weight. Excepting the diseases previously mentioned which are also associated with abnormalities of the thymus gland, it might be expected that any such chronic illness would be associated with marked involution of the thymus (Fig. 6). Thus, in patients

\*Case 4 of the present series was autopsied but examination was limited to the thorax. There was no lymphoid hyperplasia in the thorax.

The other case of myasthenia gravis in Miller's series in which no thymic tumor was found occurred in a 27-year-old white woman with a four-year history of progressively severe weakness. The thymus weighed 30 Gm. and measured 6 by 6 by 0.5 to 1.0 cm. The gland showed moderate involution. The cortex and medulla were densely packed with lymphocytes. In the medulla were definite lymphoid follicles with germinal centers. Moderate numbers of small Hassall corpuscles were present. There was no epithelial hyperplasia. Examination of the other organs showed no evidence of lymphoid hyperplasia elsewhere.

Norris<sup>31</sup> believed that epithelial hyperplasia was the chief pathologic change in the thymus in myasthenia gravis and interpreted the tumors found in myasthenia as extreme degrees of epithelial hyperplasia. Similarly, Miller<sup>14</sup> described such hyperplasia in his cases. Re-examination of the thymus glands in his cases did not show any abnormal amounts of epithelial tissue present. Instead the changes in them were similar to those in the present series.



Fig. 10.—Higher magnification ( $\times 90$ ) of Case 6 (a white woman, 34 years of age) to show lymphoid follicles with germinal centers.

In this series of ten cases, certain constant changes were present in each thymus (Figs. 7, 8 and 9). First, there was involution, although the degree of involution varied greatly. This was the so-called age involution present in all normal adult thymus glands. It consisted of a replacement of the thymic tissue by fat and a resulting separation of the lobules of the gland by adipose tissue. Secondly, the individual lobules were larger than those of the control cases, due to an increase in the numbers of lymphocytes present. In most this included a relative increase in the amount and density of the cortical tissue. In all there was an increased infiltration of the medulla by lymphocytes. In seven

4. Examination of ten thymus glands, none of which contained a tumor, removed at operation from patients with myasthenia gravis showed constant changes.

a. In all there was some age involution. This varied from a slight degree of involution to marked separation of the thymic lobules by adipose tissue.

b. In each case there was an increase in the number of lymphocytes present in the thymus. This consisted of an infiltration of the medulla with large numbers of lymphocytes and usually a relative increase in the size and density of the cortex. The normal *sharp* differentiation between cortex and medulla was lost.

c. In seven of the cases, abnormal numbers of lymphoid follicles with germinal centers were present in the medulla.

d. There was no epithelial hyperplasia and no constant change in the character and number of the Hassall corpuseles.

5. In six autopsied cases of myasthenia gravis examined which had not undergone operation there was no generalized lymphoid hyperplasia. The changes found in the thymus in myasthenia gravis were not part of such a generalized lymphoid hyperplasia.

6. The thymus was examined in individuals with Addison's disease, acromegaly, and hyperthyroidism.

a. In seven individuals with Addison's disease, the thymus of three showed changes like those in myasthenia gravis.

b. The thymus glands in five cases of acromegaly showed a striking lack of involution. In addition, two of these glands showed the changes found in myasthenia gravis.

c. In twenty thymus glands examined from individuals with hyperthyroidism, eighteen showed a striking lack of involution. In addition, the changes found in myasthenia gravis were present in five.

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with chronic illnesses of comparable duration the thymus glands are commonly much more involuted than those in patients with myasthenia gravis.

It should be emphasized that the changes found in the thymus in myasthenia gravis are not peculiar to that disease alone, for similar changes may be found in acromegaly, Addison's disease, and hyperthyroidism. It is interesting that these conditions are often associated with muscular weakness and that myasthenia gravis has been reported as occurring with hyperthyroidism.<sup>35, 37, 38, 39</sup>

Examination of the thymus in seven individuals with Addison's disease showed three in which changes occurred like those described in myasthenia gravis. In a fourth case there was a tumor of the thymus containing both lymphocytes and epithelial cells. Large lymphoid follicles with germinal centers were present in the tumor. Two cases occurred in children 3 and 4 years of age. The thymus glands appeared normal. In the seventh case, that of a 28-year-old white female, the thymus was markedly involuted and there was apparently no increase in the number of lymphocytes present.

The thymus was examined in five cases of acromegaly. Here the striking change was the lack of involution in all these glands. This was very much less than that found in the thymus glands of patients with myasthenia gravis. In addition, two of the glands showed the increase of lymphocytes found in myasthenia gravis.

Twenty thymus glands from individuals with hyperthyroidism were examined. In eighteen of these there was again a striking lack of involution. Five showed, in addition to a lack of involution, the changes found in myasthenia gravis (increased lymphocytes). Two glands showed a degree of involution within the limits of normal, but in these cases the epithelial hyperplasia in the thyroid was slight. Only one of the two patients received Lugol's solution.

#### SUMMARY

1. Examination of 350 thymus glands, of which 150 were removed from patients dying suddenly, confirmed the well-known facts about the anatomy, histology, and involution of the thymus.

2. Of the 150 thymus glands examined in patients dying suddenly, fourteen were found to contain lymphoid follicles with germinal centers in the medulla.

3. It was impossible to set up significant standards of weight for the normal thymus since great variations were found in the weight, the amount of thymic tissue, and the amount of adipose tissue present. Hence, the weight of the thymus as an index of pathologic change was considered to have little value. The ten thymus glands in this series of patients with myasthenia gravis apparently were no larger than many normal glands.



4. Examination of ten thymus glands, none of which contained a tumor, removed at operation from patients with myasthenia gravis showed constant changes.

a. In all there was some age involution. This varied from a slight degree of involution to marked separation of the thymic lobules by adipose tissue.

b. In each case there was an increase in the number of lymphocytes present in the thymus. This consisted of an infiltration of the medulla with large numbers of lymphocytes and usually a relative increase in the size and density of the cortex. The normal sharp differentiation between cortex and medulla was lost.

c. In seven of the cases, abnormal numbers of lymphoid follicles with germinal centers were present in the medulla.

d. There was no epithelial hyperplasia and no constant change in the character and number of the Hassall corpuscles.

5. In six autopsied cases of myasthenia gravis examined which had not undergone operation there was no generalized lymphoid hyperplasia. The changes found in the thymus in myasthenia gravis were not part of such a generalized lymphoid hyperplasia.

6. The thymus was examined in individuals with Addison's disease, acromegaly, and hyperthyroidism.

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# In Memoriam

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CHARLES VIRGIL MOSBY

1876—1942

On November 9, 1942, Dr. Charles Virgil Mosby died in the Grace Hospital, Detroit, of heart disease. With his untimely passing there came to a close a career dedicated to the dissemination of medical knowledge and to the advancement of medical literature and education.

Dr. Mosby, the collateral kinsman of Colonel John S. Mosby, of Civil War fame, was born on August 18, 1876, in Nevada, Missouri. The youngest of six children, he grew up on a farm and early learned "the doctrine of the strenuous life" by which he lived and died. He entered the old St. Louis College of Physicians and Surgeons and was graduated in 1899, paying his way through school by selling medical books. Following his graduation, he entered medical practice and after two years gave this up to devote all his efforts to the medical publishing field. The aspiration, kindled during his medical student days, to further medical knowledge through faithful recordings of experienced observers and to enrich medical literature with stimulating thought and advances, rapidly developed into a crusading spirit. With this firm conviction, he established, in 1901, the publishing firm which bears his name and launched his first book, *The Golden Rules of Surgery*, by A. C. Bernays, well-known St. Louis surgeon. The tremendous success of this endeavor assured him of his hopes and added impetus to his desires.

Imbued with the spirit of propagating medical knowledge, Dr. Mosby traveled far and wide exhorting eminent medical educators to widen the scope of their teachings by writing textbooks which could be at the disposal of greater numbers of students and physicians. Dr. Mosby has stimulated the publication of hundreds of books, in addition to which he founded eight medical journals and one dental journal. It was Dr. Mosby's belief that "medicine and surgery would still be primitive crafts had it not been for a few dauntless souls who were willing to record faithfully by the written word the result of their findings," and with this courageous spirit he constantly extended the frontiers of American medical and dental education.

In addition to his publishing enterprise, he found time to write philosophic dissertations and biographical essays. Among the better known of these are *Making the Grade*, *Little Journeys to the Homes of Great Physicians*, *William Beaumont—Physiologist*, *Augustus Charles Bernays—Surgeon* and *Williams McKim Marriott—Pediatrician*. For these contributions and in appreciation of his unceasing efforts and his prolific and fructiferous activities in the publishing field, he was awarded an honorary doctor of science degree by the Bates College, Lewiston, Maine.

Dr. Mosby was one of the pioneer exponents of enhancing the qualitative contributions of carefully selected authors by presenting them in a style sufficiently attractive that they would receive the full meed of attention which they justly deserved. Dr. Mosby had the knack and appreciated the importance of presenting the printed page to the eye of the reader in such a manner that the information which the author strived to convey could be more easily comprehended with the least amount of ocular effort. He possessed the ability happily to combine literary creations which were both meritorious and at the same time pleasing to the artistic sense of the medical book lover. Because of his consistent appreciation of these all-important requisites and desiderata, his work in building epoch-making medical publications will long endure as an outstanding example of what may thus be accomplished.

All who knew Dr. Mosby, and his friends were legion, were forcefully impressed with his sterling human qualities, his indomitable resoluteness, his indefatigable energy, his untiring industry, and his idealistic attitude tempered by a realistic zeal. His clear penetrating eyes, determined chin, and pleasing countenance vividly reflected his beneficent cordiality, his contagious enthusiasm, and his innate integrity. All of these admirable characteristics were harmoniously blended to distinguish his charming and generous personality and to instill immediate and reassuring confidence. Indicative of his magnanimous character is his expressed gratification of his intense interest in his work, best exemplified by his own words: "Not for tons of gold would I exchange the friends I have made in American medicine and throughout the medical world."

He is survived by his widow, Mrs. Margaret Cavanaugh Mosby, a brother, William C. Mosby, a daughter, Mrs. Highland Mary Wood, and a son, John C. Mosby.

Admired by his associates, respected by his colleagues, and loved by his intimate friends and relatives, Dr. Mosby will always remain in the minds of those who worked with and knew him well as a diligent, earnest, and sedulous co-worker and a kind, tolerant, and inspiring leader. With his passing the country has lost a loyal and esteemed citizen and American Medicine and Dentistry, an altruistic and progressive literose devotee.

# SURGERY

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## Original Communications

### SURGERY OF THE SPLEEN IN BLOOD DYSCRASIAS

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*(From Surgical Service A in the Medical School and Hospital of the University of Pennsylvania)*

IT IS our purpose to limit the scope of this presentation to the blood dyscrasias that are favorably affected by surgical procedures directed on the spleen, i.e., splenectomy, or indirectly upon its blood supply by ligation of its vessels. Justification of these procedures must be evaluated by the mortality and the morbidity following such treatments. Splenic surgery has been employed sporadically since before Christ and, later on, occasionally and specifically for the purpuras, splenic anemias, and the ictero-anemias with fairly good results. The field, however, was broadened disastrously when pernicious anemia, leucemia, aplastic anemia, toxic infections, allergies, drug anemias, etc., were included. Such injudicious surgery produced either a high mortality or left the surviving patient usually worse for the experience. In the last twenty to twenty-five years, with a more rational selection of cases and improved pre- and post-operative care, splenectomy has earned a foremost place in the treatment of splenic anemia, idiopathic or essential thrombocytopenic purpura, and hemolytic ictero-anemia. An attempt will be made, therefore, to present the facts and evaluate surgery on patients suffering from one or the other of these three conditions.

#### SPLENIC ANEMIA

Osler defined this condition as "an intoxication of unknown origin characterized by great chronicity; progressive enlargement of the spleen which cannot be correlated with any known cause, anemia of the secondary type with leucopenia, a marked tendency to hemorrhage, particularly from the stomach (esophagus), and in many cases a terminal state with cirrhosis and jaundice." Much work has been done in this field since then (1900), and yet we are, after extensive work by the pathologist and hematologist, still in the dark concerning the etiology. This ignorance of etiology is an important point in diagnosing the pa-

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tient with the above pathologic and physical findings. In other words, the diagnosis today continues to be one of exclusion before surgery should be practiced. The Banti's syndrome with a known etiologic factor justifies medical and not surgical treatment.

In the last ten years writers have attempted to explain this picture in various ways. Thompson, from the Spleen Clinic at the Presbyterian Hospital, New York City, on a series of sixty-eight splenectomies for this condition, draws the following conclusions: (1) It results from a variety of lesions that produce a hypertension in the splenic vein; (2) it is purely a mechanical congestion; (3) cirrhosis of the liver is only one obstructive cause which, if not existent at the time of splenectomy, will not develop subsequently; (4) suggests we designate the syndrome as a congestive splenomegaly in place of the old term Banti's disease. Drenckhahn is inclined to think that if the viscosity of the blood in these cases is lowered by venesections, the hemorrhages will be less frequent and less massive. Whipple, in 1937, reported thirty-one cases of Banti's disease with fifteen of unknown etiology. He felt then that portal hypertension was the factor to investigate. One of us (E. L. E.) found twenty splenomegalies in patients with anemia at the Philadelphia General Hospital in the last five years, two of which were diagnosed splenic anemia (Banti) and eighteen of which were classed as of undetermined origin. Davidson (1934) showed that the blood picture was not reliable, stating that the red blood corpuscles and hemoglobin can be restored to normal with iron.

*Treatment.*—Howells reports ninety-four cases and compares the medical and surgical results (Table III). Splenectomy in fifty-one patients gave improvement in 43 per cent; medical care of forty-three patients gave 46 per cent improvement. He further found that in both types a hemoglobin of 60 per cent + accompanied improvement in an average of 59 per cent, whereas if the hemoglobin was between 30 and 60 per cent, the average improvement in both instances was only 33 per cent. His conclusions were that splenectomy does not improve the expectancy of life nor prevent the progress of the cirrhosis or the anemia or the recurrence of hematemeses. Therefore, "it is illogical to retain it as a routine method of treatment." Again, of thirty-one patients, Whipple (1937) had eighteen live, one as long as eleven years. His experience was that of the patients who had preoperative hemorrhages, eleven in number, seven died from hemorrhage. His conclusion was that splenectomy increases life expectancy but does not alter the condition of patients with hemorrhage and is not advisable in severe anemias. Wada (1941) states that in his series of seventeen cases of Banti's disease, the operative mortality in patients with early cases was nil, whereas in patients with the delayed cases it was 40 per cent. Pemberton, in 1931, in a series of 167 cases, found that ninety-eight of the patients had history of preoperative hematemeses; twenty-nine of these, or 29 per cent, died from hematemeses and only nine from thrombosis. He also found one patient

lived nineteen years and ten lived over nine years. This same clinic found that 50 per cent of their patients bled before operation and also after operation. Whipple, quoted by Rives, has now 107 splenectomies to his credit, fifty-six of which were for splenic anemia. Ranzi, in 1936, reported twenty-one cases. Of the fifteen patients followed, one was well after twenty years, two were not benefited, and seven were well from two months to two years. Evans states that one-half of his patients had recurrence of hematemesis, with several deaths.

Eliason and Johnson, in 1937, reported cases of twenty-one patients. Seven of the deaths were directly due to liver damage, three of these had hemorrhage; of the survivors, one lived eleven years, two lived seven years, two lived five years, two lived three years, etc.

Diamond, in 1938, reported eight cases in children diagnosed as splenic anemia, by reason of splenomegaly of unknown origin, chronic progressive hypochromic anemia, a constant leucopenia, and thrombocytopenia. Splenectomy was followed by a rapid rise in the leucocytes, an elevation of the platelet level, and a permanent improvement in the anemia. Six of the eight have remained well for from six to ten years, with no evidence whatever of the disease. These results can be viewed with great satisfaction.

Pemberton (1940) reports on splenectomy in 215 patients with splenic anemia and Banti's syndrome with a hospital mortality of 9.8 per cent but with a most gratifying life expectancy record: 54.6 per cent lived five years +; 41.5 per cent lived ten years +; and 20.4 per cent lived twenty years or more. His experience is that 50 per cent of patients with hemorrhage before operation also bled subsequently despite the employment of one or more of the indirect methods of vessel ligations or omentopexy.

Rousselot (1938) from the Spleen Clinic in the Presbyterian Hospital, New York City, reports fifty-five patients with Banti's syndrome which condition is termed congestive splenomegaly, therein including Laennec cirrhosis, 14 with 4 deaths; cirrhosis unclassified, 2 with no deaths; schistosomiasis, 11 with no deaths; and obstructive factor undetermined, 13 with 3 deaths; also cirrhosis unclassified and thrombosis, 3; portal vein transformation, 2; and stenosis of portal vein, all with no deaths. Further statistics will appear in the Tables I, II, III, and IV.

In our series of twenty-eight patients treated by splenectomy, there was a mortality of 25 per cent; 28 per cent of the survivors lived five years and 21 per cent lived ten years.

It is to be noted from a study of Table IV that the mortality figures ranged from 0 to 40 per cent. This would seem to indicate that some factors, probably the degree of cirrhosis and liver damages, varied greatly. This was the case in our series, seven of the eight patients who died having extensive damage to the liver.

Ligation of coronary vein, splenic vein, artery or pedicle, and injection of esophageal varices have been done in a few cases only and with

TABLE I  
SPLENIC ANEMIA (BANTI)  
CONGESTIVE SPLENOMEGALY

AUTHORS	SPLENECTOMY	HEMORRHAGE	
		PREOP. (%)	POSTOP. (%)
Thompson	68	40	59
Whipple (1931)	31	73	63
Pemberton (1931)	167	50	50
Pemberton (1940)	215	59	50
Rousellot (1939)	55	?	12
Diamond*	11	?	50
Evans	?	?	50
Eliason and Stevens (1942)	28	7	35

\*Children.

TABLE II  
SPLENIC ANEMIA  
FOLLOW-UP DATA

AUTHORS	5 YR. (%)	10 YR. (%)	20 YR. (%)
Pemberton (1940)	55+	43+	22+
Ranzi (1936)	5+	5+	4+
Diamond (1938)	75	75	—
Rousellot (1939)	20	10+	—
Whipple (1937)	58+	58	—
Eliason and Stevens (1942)	28+	21+	—

Eighty-nine per cent returned for follow-up.

TABLE III  
SPLENIC ANEMIA MORBIDITY  
MEDICINE VS. SURGERY

		HGB. %	AVERAGE IMPROVEMENT	% IMPROVEMENT
51 Surg. 43 Med.	Group I	60+	30 { Surg. Med.	43 63
	Group II	30 to 60	33 { Surg. Med.	30 39
	Group III	Below 30	31 { Surg. Med.	31 33

TABLE IV  
SPLENIC ANEMIA MORTALITY

AUTHORS	(%)
Pemberton	12.4
Ranzi	40
Diamond	25
Andrus and Holman	0
Rousellot	14.5
Eliason and Stevens	25



only indifferent results, which seems to show that persistence of varices after operation dooms the patient and nothing will correct them. Rhoads and Stein report a case in a child in which the varices were definitely reduced following the triple procedure of splenectomy and ligation of both the gastric artery and the coronary vein.

*Conclusion.*—Splenectomy gives the patient the best chance. The earlier in the disease that splenectomy is done, the lower the surgical mortality and the greater the life expectancy. It is the opinion of one of us (E. L. E.) that this is the only choice, even with cirrhosis. The operative mortality should not be over 10 per cent at the worst, and some of the patients have lived twenty years.

#### PURPURA HEMORRHAGICA

Under this heading the surgeon is concerned only with essential thrombocytopenic purpura, and for this reason it is important for our hematologists and medical colleagues to eliminate the innumerable other causes of purpura before advocating splenectomy. The consensus of opinion today is that the findings in the essential group are petechial hemorrhages and bleeding from the mucous membranes, low platelet count, prolonged bleeding time, normal coagulation time, delayed or absent clot retraction, a secondary anemia with evidence of regeneration, a normal or increased total white count with a normal differential count, a positive tourniquet test, and a spleen that may or may not be enlarged.

Errors in diagnosis are more frequently made in patients with leukemia and aplastic anemia with purpuric phenomena due to allergies, drugs, particularly sedormid, etc.

Essential purpura as it confronts the surgeon may be divided into four groups.

Group I: Mild or moderate bleeding in the initial attack. Conservatism and possibly transfusions are all that are necessary for a high per cent of permanent cures.

Group II: Mild bleeding with recurrent attacks. Here again there is almost uniform agreement that, conservatism failing, splenectomy is definitely indicated.

Group III: The fulminating type in the initial attack. Here we have the most difficult problem of all. Up to 1932, when a survey was made of the literature by Eliason and Johnson, in thirty-five patients the mortality was 34.3 per cent. In the next twenty-one patients reported up to 1936, the mortality was reduced to 13.6 per cent, and yet in 1936 Giffin reports a 50 per cent mortality and Whipple, in 1937, mentioned seven deaths in eight patients with fulminating cases. McLean and Amessee each report a high per cent of deaths. Rosenthal, in 1939, in an analysis of 153 cases, states that splenectomy is contraindicated in acute purpura in children, in acute purpura with fever and leucocytosis, and in megakaryophthisis. He found a high per cent of the patients with acute cases (thirty-eight) recovered spontaneously.

It is still difficult to evaluate the findings due to lack of data, but it is not unlikely that the high mortality has been due to delayed splenectomy and insufficient postoperative care. Possibly, due to greater knowledge on the part of our hematologists and the expansion of blood banks, the mortality of the last two or three years may prove to turn out much lower.

Group IV: Severe bleeding in recurring attacks. These patients having shown by their history that they have survived by reason of remissions should be treated accordingly by transfusions as long as they improve by this regime. However, should such not be the case, splenectomy is indicated at once.

The results following removal of the spleen for purpura hemorrhagica have been so satisfactory that when the disease is an inconvenience and has not responded to nonoperative treatment, a splenectomy should be advised. According to reports up to 1932 (Eliason and Ferguson), 87 per cent of 179 with follow-up reports were thus cured. Unfortunately, there was a woefully short follow-up in many instances. Pemberton, in 1934, with long follow-up periods, reported 63 per cent as permanently cured by ectomy. Giffin, back in 1927, stated that he has never seen purpura persist after splenectomy coupled with a conscientious elimination of foci of infection (Table V). Vaughan (1939) reports six patients all surviving from ten to fifteen and one-half years after splenectomy and states that "these six bring the total reported cases to fifty-nine patients living from five to fifteen and one-half years after operation." Diamond in his study of twenty-eight cases in children states that this disease tends to be more acute in children than in adults. Eight of these had a splenectomy performed after other measures had failed; six of these were completely relieved and have maintained normal platelet counts since then. Two were only moderately improved; of the twenty treated medically, twelve have had spontaneous and permanent remissions; six continue with occasional bleedings and permanent low platelet counts. Two died from intracranial hemorrhages. His advice is to advocate surgery only in the severe cases (Table VI).

Thomas (1927), with his sixty-two patients, reached the same conclusion.

TABLE V  
PURPURA HEMORRHAGICA  
FOLLOW-UP DATA

AUTHORS	5 YR. (%)	10 YR. (%)
Literature (1932)	87	
Pemberton (1934)	63	
Vaughan (1939)		6 cases
Pemberton (1940)	89	87
Rousellot (1938)	42	19
Eliason and Stevens (1942)	50	21

One hundred per cent returned for follow-up.

TABLE VI  
FULMINATING PURPURA HEMORRHAGICA

AUTHORS	MORTALITY (%)
Literature (1932)	34.3
Literature (1936)	13.6
Giffin (1936)	50
Amese	High
Whipple (1937)	87
McLean (1937)	High
Diamond (1938)	25
Andrus and Holman (1939)	0
Eliason and Stevens	0

Pemberton (1940) performed splenectomy for purpura on eighty patients with hospital mortality of 8.8 per cent and a five-year survival of 89 per cent and a ten-year survival of 87 per cent. He, of course, adheres to his 1933 statement; namely, "In the treatment of purpura of mild severity, splenectomy is not recommended until other measures fail. Since in the acute forms the dangers of delay outweigh those of operation and since splenectomy is the surest cause of remissions, commonly complete and permanent, such should be the treatment." Elliott (1938) reports from the Spleen Clinic twenty-one patients with splenectomy for idiopathic purpura with no operative deaths and with nine known five-year cures and four ten- to eighteen-year cures. Eleven patients all operated upon less than five years are living and well. Expressed further, they found that splenectomy gave satisfactory results in 85.7 per cent, and conservative treatment of twenty other patients gave satisfactory results in only ten per cent of the cases (Table VII).

TABLE VII  
PURPURA HEMORRHAGICA  
SURGICAL MORTALITY

AUTHORS	NUMBER OF CASES	MORTALITY (%)
Diamond	5	0
Pemberton (1940)	80	8.8
Elliott (1938)	21	0
Eliason and Stevens (1942)	15	6.6(?)*

\* (?) Only death error in diagnosis

*Conclusion*—Mild purpura does not require splenectomy until other measures fail. Acute purpura should be treated by early splenectomy as the surest and safest course to pursue, both as to mortality and morbidity.

#### HEMOLYTIC JAUNDICE

Hemolytic jaundice, also termed ictero-anemia (acholuric jaundice) for many years, was classed as congenital or acquired. Of recent years, this differentiation has less and less followers, it being felt that they are one and the same. It does seem, however, to other clinicians that there is good reason to continue to differentiate them.

Hemolytic ictero-anemia is characterized by the finding of secondary anemia of a microcytic type, reticulocytosis, increased fragility of the red blood cells, spherocytosis with the volume normal or increased, acholuric jaundice, and an elevated icterus index and splenomegaly. There is no itching of the skin in this type of jaundice. The congenital type appears in infants and children. The acquired form usually appears after 20 years of age, is more severe, and has exacerbations or "crises" of malaise, abdominal pain, increased jaundice with the associated blood findings, more pronounced anemia, fever and rapid increase in the splenomegaly, accompanied by abdominal pain. The high incidence of associated biliary calculi, 60 per cent, adds a confusing and complicating feature to this otherwise clear diagnosis. Whereas the stools in ictero-anemia have normal amount of bile, a complicating stone obstruction in the common duct renders them acholic.

Doan found the conditions existing in thirteen families, twelve of whom had no knowledge of it, although one member in each generation had it. The importance of recognizing that constitutional defect lies in the fact that a fatal relapse or exacerbation may be precipitated by an infection or trauma at any time. Diamond reports on the study of twenty-five cases of this disease in children. In five, operation was refused with resultant death in two. Splenectomy was done in twenty, of whom eighteen have been completely relieved of all symptoms; one died of mesenteric thrombosis and one was relieved but not cured. He feels that this disease in children may not progress in as benign a fashion as it often does in adult life; also, that the younger the patient at the onset, the more severe the condition tends to become. The infant with the disease may not be able to wait for a second crisis before a splenectomy is performed. In children, delay also spells growth disturbances in the skeleton and other organs, even mental retardation as well as gallstone formation. Early splenectomy is indicated. Pemberton (1940) reports 165 patients with hemolytic icterus treated by splenectomy with a hospital mortality of 3 per cent and a most enviable survival record, namely, 88 per cent five-year and an 80 per cent ten-year survival rate (Table VIII).

The treatment for this condition is splenectomy which produces phenomenal results; that is, permanent and positive cure. Care must be

TABLE VIII  
HEMOLYTIC JAUNDICE MORTALITY

AUTHORS	MORTALITY (%)
Pemberton (1931)	3.4
Doan (1934)	0
Pemberton (1940)	3
Diamond (1938)	5
Andrus and Holman	0
Rousellot (1938)	6.6
Eliason and Stevens (1942)	0

taken, however, to have an indubitable diagnosis. Atypical cases are not helped by surgery on the spleen. It is much wiser to operate upon these patients in the remission period, although the surgeon's hand may be forced by the rapid uncontrolled acute phase. Doan mentioned seventy-five blood relatives with recognized trait in forty. Seventeen of these had a splenectomy done, five of whom had a blood count of only one million. There were no deaths despite the fact that medical care has accomplished nothing except to bring the patient to surgery in a precarious condition. It has frequently been shown that patients can live with this chronic state of anemia due to continued hemolysis for many years relatively normally so one should not rush into surgery. We saw a young woman of this sort who had reached the age of 35 years and had had four children and was pregnant again when seen by us.

Removal of the spleen was first done for this condition fifty-five years ago. This patient is known to have lived forty-five years.

Thompson (1938) also reports from the Spleen Clinic in New York thirty splenectomies for this disease with an operative mortality of two, or 6.6 per cent, with an excellent result in this condition in twenty-six of the others for follow-up periods ranging from one to eighteen and one-half years. Biliary calculi were found at operation in four of the patients in this group. Thirteen cases treated conservatively were all found unimproved in follow-up reports ranging from 7 to 39 years (Table IX).

TABLE IX  
HEMOLYTIC JAUNDICE  
FOLLOW UP DATA

AUTHORS	5 YR. (%)	10 YR. (%)	45 YR.
Pemberton (1940)	89.3	80.4	1
Diamond (1938)	90		
Literature			
Rousellot (1938)	26	10	
Eliason and Stevens (1942)	50	15	

Ninety per cent returned for follow-up

He concludes that splenectomy promptly, completely, and permanently relieves these patients but that this operation does not benefit the atypical hemolytic anemias.

*Conclusion*—The above data indicate that splenectomy is the treatment of choice in true, congenital ietero-anemia. In the acquired or adult form, mild in character, splenectomy is not necessarily the treatment indicated.

#### TECHNIQUE

The operation of splenectomy may be a very difficult one or a relatively simple one, depending upon the size of the spleen and the presence or absence of adhesions. The left rectus incision is probably the most frequently used. The lower pole of the spleen is delivered first and brought

out of the wound. The upper pole of the spleen then may be exposed. By using this procedure, the size of the incision need not be so large as would otherwise be required. When the spleen is very large, it may occasionally become necessary to make a lateral transverse extension of the incision at the lower end. This gives considerable additional exposure. Such a step is seldom required but may be a valuable aid when an especially large spleen is encountered. Some surgeons find the left paramedian or the left subcostal incision preferable to the left rectus incision.

By means of the gloved finger, the spleen is freed posteriorly. In this manner the capsule is not torn. The lienorenal ligament may occasionally have to be nicked with an instrument. The lower pole of the spleen is separated first and brought out of the incision. As this is done, the upper part of the spleen can be exposed. When the posterior attachment has been completely freed, the spleen is turned up to expose the posterior aspect of the pedicle devoid of a peritoneal covering. The peritoneum is then slit over the anterior aspect of the pedicle and the splenic vessels are exposed. Care must be taken that the tail of the pancreas, the stomach, and the retroperitoneal duodenum are sufficiently pushed aside before hemostats are applied. The vessels are clamped close to the spleen which is then removed. The vessels are doubly ligated. Wise has suggested the use of a rubber-shod clamp across the entire pedicle until the vessels are ligated individually. It would seem that he has minimized the possibility of damage to the pancreas by this procedure. The oozing from the bed of the spleen is usually so insignificant that no drainage is necessary. When the ooze is sufficient, a Penrose drain may be inserted. The drain is best brought out through a stab wound lateral to the incision.

When a large spleen has been removed, an abdominal binder is applied immediately to help maintain abdominal pressure. Pitressin is given every fourth hour for the first forty-eight hours. The convalescence may be marked by a moderately febrile course which is frequently quite prolonged. This is probably due to a thrombophlebitis of the splenic vein as mentioned by Bryce. No deaths due to extension of the thrombosis into the portal vein have been recognized in our personal series.

#### SUMMARY

An extensive review of the literature of the last ten years has been made and a statistical report compiled showing the mortality and life expectancy following splenectomy in cases of splenic anemia, thrombocytopenic purpura and ictero-anemia. Added to these is a similar report on sixty-three personal cases.

The technique of splenectomy is discussed.

#### CONCLUSIONS

Splenectomy gives the patient with splenic anemia the best chance. The earlier in the disease that splenectomy is done, the lower the surgical

mortality and the greater the life expectancy. It is the opinion of one of us (E. L. E.) that this is the only choice with cirrhosis. The operative mortality should not be over 10 per cent at the worst, and some of the patients have lived twenty years.

Cases of chronic hemorrhagic purpura that do not respond to conservative therapy should be subjected to splenectomy. In acute or fulminating purpura hemorrhagica, if the bleeding does not respond promptly to conservative measures, splenectomy should be performed early before the patient's condition is critical. A careful elimination of infection is important in the prevention of recurrent purpura. Recurrence of a serious nature is unusual.

Splenectomy is the treatment of choice in hemolytic jaundice, particularly in children. It is preferable to perform the operation during a remission, but occasionally it is necessary to remove the spleen during an acute exacerbation. The results following splenectomy are good in a high percentage of cases. In adults splenectomy is not always necessarily indicated.

# SHOCK: THE PHYSIOLOGIC AND CLINICAL ASPECTS

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THE modern therapy of shock is based on a thorough understanding of the physiologic changes occurring in the injured patient. Peripheral circulatory failure of the hematogenic (Blalock) type is always associated with a diminution of the effective circulating blood volume whether this be due to hemorrhage, trauma, or burns. The exact mechanism producing this depletion may be in dispute, but experimental and clinical investigation has developed methods of estimating the relative amounts of fluid, protein, and red blood cells which will be lost in certain types of injury. There are definite changes which occur in the blood of the patient in shock, and some of these contribute to the development of the shock state while others probably perpetuate it. All of these factors cannot be corrected, but it is possible to attempt replacement of the fluid and protein which is lost and thus improve the circulation and overcome tissue anoxia. A fundamental premise of therapy is the realization that hematogenic shock does not develop instantaneously, and that the clinical appearance of hypotension is the gross evidence of time-consuming changes in the circulation.

In order to provide a background for rational therapy it is necessary to evaluate certain fundamental changes which occur in the circulation during the development of shock. It is not sufficient to define shock because of the variations in the theories of its mechanism; each author's definition will vary according to his personal concept, and will stress the factors which he believes most important. Blalock has considered it as "peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume of intravascular fluid." This does not condemn any one theory, and provides as thorough an understanding as our present knowledge will permit. There are four outstanding theories as to the mechanism of the fluid loss in shock: (1) local loss of blood and fluid, (2) toxemia causing generalized capillary permeability, (3) vasoconstriction, (4) nociceptive impulses. These theories have been discussed in detail in recent reviews of the subject, and no attempt will be made to analyse critically the evidence for or against them.

In spite of the disagreement over the mechanism of shock there are many physiologic changes in the circulation which are of basic importance. The decreased effective circulating blood volume has been mentioned. Freeman and others<sup>1, 2, 3</sup> have shown that there is peripheral vasoconstriction resulting in a diminished peripheral blood flow. There



is a fall in the venous as well as the arterial blood pressure,<sup>4</sup> and the cardiac output is decreased.<sup>5, 6</sup> The oxygen saturation of the blood is decreased,<sup>2</sup> and there is diminished oxygen consumption by the tissues. A large amount of plasma protein disappears from the circulation,<sup>7</sup> and because of the preponderant loss of plasma the red cell hematocrit becomes concentrated. There are other factors which may occur, but which may not be of primary significance: plasma potassium increases,<sup>8</sup> tissue anoxia develops, and there may develop a generalized capillary permeability. The role of the adrenal cortex and of tissue metabolites or toxins has not as yet been definitely established.

A great deal of confusion has arisen because of attempts to classify shock as primary and secondary. Primary shock is defined as the state of circulatory collapse which occurs almost immediately after an injury and is characterized by subnormal temperature, cool perspiring extremities, pallor, rapid pulse, and low blood pressure. This condition may occur within one-half an hour following a head injury, a perforated ulcer, or in association with spinal anesthesia or with drugs such as histamine. The patient often shows rapid improvement following relief of pain, or sometimes even without treatment. In this instance the fall in blood pressure is probably due to a rapid increase in the size of the vascular bed following capillary dilation while the blood volume remains essentially unchanged. As soon as the tonus of the peripheral circulation improves, normal circulatory balance is established, and the blood pressure rises. This condition differs markedly from that existing in the patient who gradually develops circulatory collapse several hours after injury and who is said to be suffering from secondary shock. This patient has had an actual loss of effective blood volume from the circulatory bed and the blood pressure falls in spite of compensatory peripheral vasoconstriction. Blalock<sup>6</sup> has suggested an admirable classification of shock which is of value in differentiating these types. He suggests that the term primary shock be replaced by (1) neurogenic, the fall in blood pressure resulting from pain, spinal anesthesia, etc., and (2) vasogenic, that resulting from histamine, anaphylaxis, etc. The term hematogenic is reserved for shock resulting from an actual decrease in effective blood volume.

The classification of these types of shock will not be confusing if the entire clinical picture is correlated with the type and extent of the injury and the period of time which has elapsed since the injury occurred. Unless the patient has had a rapidly exsanguinating hemorrhage, an early fall in blood pressure, with other signs of shock, may not mean serious derangement of the circulation, and the response to treatment may be very rapid. If, however, the circulation is not improved, early neurogenic shock may result in a true hematogenic type, i.e., because of the sluggish circulation, tissue anoxia may develop with resultant damage to the capillaries and an increase in their permeability. The classical signs of shock are the late manifestation of a process which

begins immediately after an injury. It is of the utmost importance to realize that the blood volume may decrease by as much as 50 per cent, and the blood pressure remain normal because of vasoconstriction. The replacement of fluid loss is of most value before the circulatory depletion has become extreme and before the shock state has become irreversible. It therefore would seem more logical to evaluate the process as a whole rather than to wait for obvious circulatory changes before instituting therapy. The prevention of profound circulatory collapse is possible in many instances in which it would be fatal to await the obvious changes. The value of the hematocrit, blood, or plasma specific gravity, and plasma protein concentration in predicting and evaluating shock will be discussed.

#### RECOGNITION OF SHOCK

1. *General Condition of the Patient.*—An accurate evaluation of the general appearance of the patient together with type and extent of the trauma form the most practical clinical method of recognizing impending shock. The degree of shock is, in general, in direct proportion to the amount of tissue damage and the time which elapses before treatment is instituted. The patient who appears apathetic, who is pale, and whose extremities are cold and clammy within a few hours after injury may already have a marked reduction in blood volume in spite of a nearly normal blood pressure.

2. *Pulse.*—The onset of shock is usually associated with a rapid thready pulse, but, both in the experimental animal and in man, a bradycardia may occur in profound shock.<sup>7</sup>

3. *Blood Pressure.*—The arterial blood pressure has long been considered the classical criterion of shock. In the experimental animal, the blood pressure may be normal at a time when the circulating plasma volume is half the normal, only to fall precipitously just before death.<sup>7, 9</sup> That the arterial blood pressure is an unreliable guide has long been recognized, because the vascular bed is gradually decreased by vasoconstriction until the vasomotor center fails and collapse occurs. Although the venous pressure decreases as shock develops, it must be considered an unreliable clinical guide. The hydrostatic pressure of the vein, the muscle pressure,<sup>10</sup> and the slowed peripheral blood flow make venous pressure determinations unreliable unless performed under carefully controlled conditions. The pulse pressure is often of value in detecting early shock; as peripheral vasoconstriction occurs the diastolic pressure may increase with a consequent decrease in pulse pressure. A patient with a gunshot wound of the abdomen was found to have a 50 per cent decrease in circulating plasma volume; his blood pressure was 120/100. After recovery his normal blood pressure was found to be 120/70. This change is not always evident, but when present is significant.

4. *Hematocrit.*—The hemoconcentration associated with shock has been emphasized by Moon<sup>11</sup> and others. In shock produced by intestinal

manipulation the hematocrit rises as the plasma volume decreases.<sup>7</sup> The hematocrit is of minor significance in shock due to hemorrhage since the remaining blood is diluted by tissue fluids and the hematocrit decreases. If the shock is due to trauma or operative procedures, the hemoconcentration, unfortunately, varies in degree, and individual determinations may be of little value. A hematocrit of 45 per cent may indicate hemoconcentration in a patient who has an anemia, but this would not be evident unless a control determination were available. If the hematocrit is markedly increased the individual determination is of value, but if not, the trend of at least two determinations must be known. It thus becomes of limited value in the evaluation of a patient in the accident ward. The hemoconcentration of the burned patient is of unquestionable value, and this will be discussed later.

5. *Plasma Specific Gravity and Plasma Protein Concentration.*—Seudder<sup>8</sup> has emphasized the increase in plasma and blood specific gravity which occurs in shock, and he feels that this can be used in the clinical evaluation of the shocked patient. The specific gravity of plasma will not increase unless more fluid than protein is lost from the circulation, and dehydration is not the outstanding feature of shock during the early stages. Large amounts of protein are lost from the circulation whether the shock is due to trauma or burns, and this loss may occur so rapidly that the plasma specific gravity decreases rather than increases. In experimental shock produced by intestinal trauma the specific gravity decreases (Fig. 1). This decrease has been uniform in

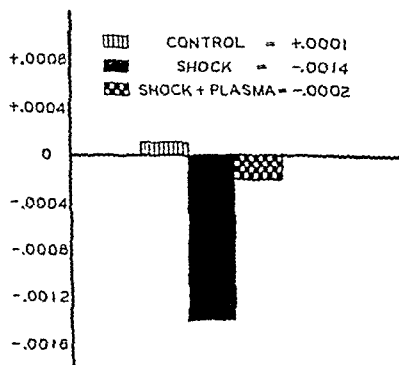


Fig. 1.—Graph showing specific gravity in experimental shock.

all of the experiments in which the animals developed peripheral circulatory failure, and in general the most marked fall of the specific gravity occurs in the animals most profoundly shocked. When these animals are treated with plasma, the rise in blood pressure is usually associated with an increase in the plasma specific gravity.

Specific gravity determinations have been done at frequent intervals during abdominal operations which resulted in varying degrees of peripheral circulatory failure. The specific gravity has shown a definite

tendency to decrease with the development of shock when no fluid therapy was given. The patients who were in shock and received adequate plasma replacement therapy responded with an increase in or maintenance of the specific gravity. In early burn shock the plasma specific gravity may also decrease. In our experience it has been difficult to prevent the specific gravity from falling by administering adequate plasma, and the problem of increasing plasma protein concentration has not occurred. If a burn has been neglected, secondary dehydration may develop, but this is not a factor in the initial treatment. The initial loss of protein in and around the burned area is so great that the plasma specific gravity decreases. This should not be confused with the concentration of the hematocrit, but should be considered as a separate change.

#### TREATMENT OF SHOCK

The importance of the early recognition of impending shock has been stressed because it is in the early stages that replacement therapy can be most effectively accomplished. The decreased blood pressure of hematogenic shock develops only after there has been a marked decrease in blood volume and the circulation is no longer able to compensate by peripheral vasoconstriction. If the blood volume can be replenished before this advanced stage is reached, many of the deleterious effects of peripheral circulatory failure may be avoided, and the patient will respond more favorably. The injured patient should be treated as soon as possible; an hour's delay may mean the difference between irreparable circulatory damage and compensable impending failure. The compound fracture should not be débrided or the burn treated locally until blood or plasma is available and intravenous injection started. One of the greatest errors of clinical judgment is to underestimate the seriousness of an injury, and to have the patient develop the classical signs of shock on the operating table without having received adequate shock therapy. The ease with which blood or plasma may be preserved no longer permits the excuse that proper fluid was not obtainable.

The treatment of shock may be divided into two main categories: (1) General features including oxygen and drug therapy, and (2) fluid replacement.

*General Features.*—The injured patient should be made as comfortable as possible and small doses of morphine are not contraindicated after the extent of the injury has been determined. Major bleeding should be controlled and compound fractures should be temporarily immobilized to prevent further damage to the soft tissues. The patient should be kept warm, but Blalock and Mason<sup>12</sup> have shown that overheating may be deleterious. At the present it seems most advisable to conserve body heat by means of blankets, etc., but excessive external heat is contraindicated. The foot of the bed or stretcher should be elevated to promote venous return from diminished peripheral circula-

tion. The administration of a high concentration of oxygen is of value in combating the anoxemia of shock. Wood, Mason, and Blalock<sup>12</sup> have demonstrated experimentally that an increase in oxygen content of arterial and venous blood is beneficial in the shocked animal, and clinical experience has confirmed their observations.

The use of vasopressor drugs such as adrenalin and ephedrine should be discouraged. Freeman and others<sup>2</sup> have shown that shock may be produced by prolonged administration of adrenalin. Compensatory peripheral vasoconstriction is already present in hematogenic shock, and further constriction may lead to increased capillary stasis and anoxemia. Small amounts of ephedrine or adrenalin are permissible in the early neurogenic shock, but the patients should be carefully selected.

Adrenal cortical extract is being recommended in shock on the theory that it will prevent or decrease capillary permeability. The work of Swingle and others<sup>14, 15</sup> has resulted in favorable reports of its efficacy. Rhoads<sup>16</sup> has used adrenal cortical extract in conjunction with plasma in treating burned patients. Their results indicate that less plasma is required to maintain the blood volume if adequate adrenal cortical extract is used. Although these results seem definite, the response of the burned patient is variable, and great care must be taken in evaluating clinical results. This is by no means a condemnation of the extract, but merely a reservation of final opinion until this method of treatment has withstood the test of extensive clinical evaluation. In our clinic, burns of apparently equal severity have been treated with and without the extract with no appreciable difference in protein and fluid requirements. If there is a generalized increase in capillary permeability in secondary shock, the method is sound; if all the fluid is lost at the site of the damaged capillaries it would seem of less value.

*Fluid Replacement.*—The most fundamental aspect of the present-day treatment of shock is the replacement of the various elements lost from the circulation. The proper treatment demands an understanding of the relative proportion of red cells, fluid, and protein which are lost in various types of hematogenic shock. Fig. 2 is a schematic representation of the relative amounts of the three elements present in the blood stream when the decreased blood pressure is due to (1) dehydration, (2) hemorrhage, (3) trauma, and (4) burns. The electrolytes and other components of the plasma are disregarded for purposes of simplicity. The dehydrated patient requires only the parenteral injection of normal saline solution. The total circulating protein and red cells have not been depleted.

When the blood volume is depleted by hemorrhage the protein, fluid, and red cells are lost in the same proportion as they existed in the blood. If the hemorrhage has been minor, the volume may be restored with saline solution or, if more extensive, whole blood should be used.

The body will tolerate extensive loss of red cells, but a serious hemorrhage may result in a serious loss of protein. If the circulation is restored with plasma, red cells may be mobilized from areas of stagnation or reserve sources. Brennan<sup>17</sup> has shown that an actual increase in circulating red cells may result from plasma injections following hemorrhage. Slow prolonged hemorrhage may result in the visceral changes of traumatic shock, and require the same type of treatment.

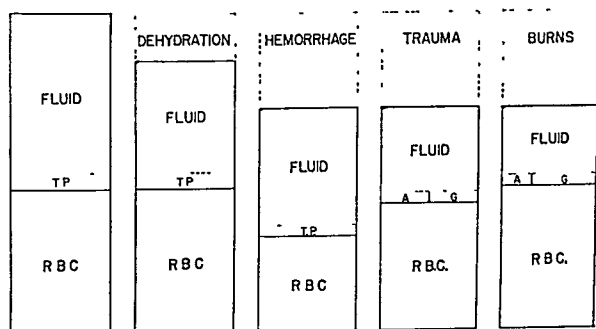


Fig. 2—Schematic representation of shift of blood components in shock.

In traumatic shock whole blood is lost at the site of injury, but there is an excessive loss of plasma from the damaged capillaries. Consequently, the total volume of red cells may be decreased, but the most marked decrease occurs in the fluid and protein elements of the circulation. Actual determinations of the plasma volume may indicate a 50 per cent reduction of fluid. Although the concentration of circulating plasma protein may be normal or only slightly decreased, the total circulating protein is greatly reduced. The intravenous injection of saline solution is detrimental. The saline solution causes dilution of the remaining protein and a resultant decrease in colloid osmotic pressure. It may cause a temporary increase in blood pressure, but the increased hydrostatic pressure will result in further protein loss and more profound shock. Plasma or whole blood should be used in traumatic shock to replace adequately the depleted circulation. The large amounts necessary must be emphasized, as 1,500 or 2,000 c.c. of blood or plasma are often required to replenish the blood volume of the adult in shock.

The shock resulting from burns is almost entirely due to plasma loss in the vesicles of the burn and in the underlying tissues. The volume of red cells remains essentially unchanged and the hematocrit increases. The plasma volume is greatly reduced and a tremendous amount of plasma protein is lost. The fluid in the vesicles contains 4 to 5 Gm. per cent of protein. Since about 90 per cent of this protein is albumin, an inversion of the albumin-globulin ratio results. It is of interest to note that in recently burned patients the loss of protein is so great that the plasma specific gravity and protein concentration decreases.

For this reason, the burned patient requires very large amounts of plasma to replenish the fluid and protein. Saline injections are as deleterious in burns as in traumatic shock because of protein dilution and resultant edema.

A comparison of the response of two burned patients to fluid therapy emphasizes the importance of carefully analyzing the changes as they occur in the circulation. Patient G. S. (Fig. 3) was admitted to the hospital in profound shock with second- and third-degree burns of the

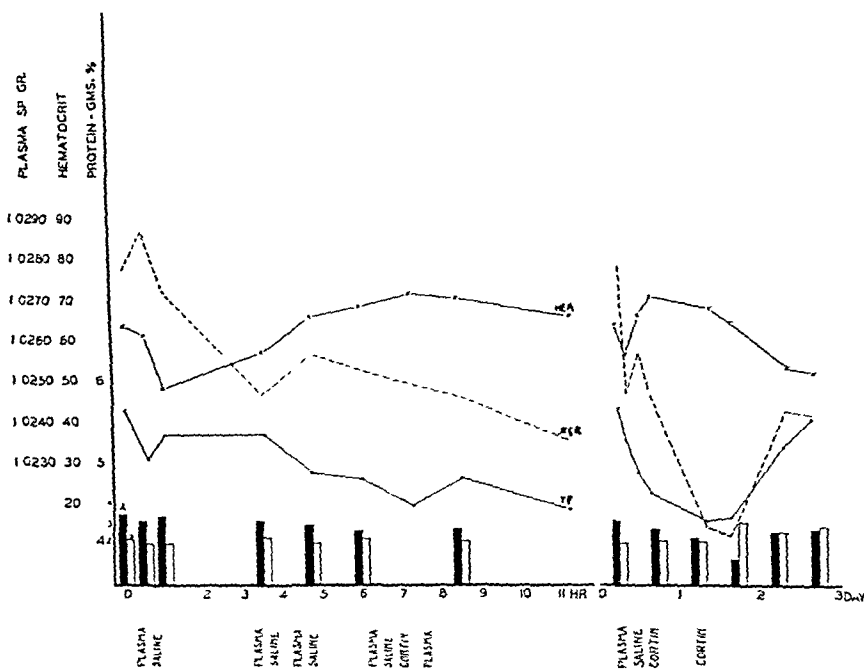


Fig. 3.—Graph of hematocrit and plasma levels after extensive burns in Patient G. S.

entire trunk, face, neck and both arms. The severity of the shock is indicated by the fact that his blood pressure did not reach a normal level for thirty-six hours in spite of intensive fluid therapy. This patient received a total of 2,200 c.c. of plasma and 6,600 c.c. of saline solution during the first twenty-four hours with a resultant marked decrease in the plasma specific gravity. His condition was so serious that it was impossible to adequately débride and treat the burned area; however, tannic acid and silver nitrate were applied to decrease local fluid loss. Actually he required an amount of fluid greater than his entire blood volume to maintain the circulation in spite of the use of adrenal cortical extract. It is obvious from the decrease in the plasma specific gravity and protein concentration that he should have received much more protein and less saline solution. The albumin-globulin ratio became inverted by the second day, and this is due to the greater loss of albumin than globulin in the burned area. This case also illustrates

the possibility of error inherent in the specific gravity determination of protein concentration. Plasma protein analyses were performed by the micro-Kjeldahl method as a check on the specific gravity. There is a close relationship between the results obtained by the two methods when the albumin-globulin ratio is normal, but the specific gravity interpretation is less accurate when the albumin-globulin ratio is reversed. The hematocrit remained concentrated during the first twenty-four hours, but on the second day returned to the normal level.

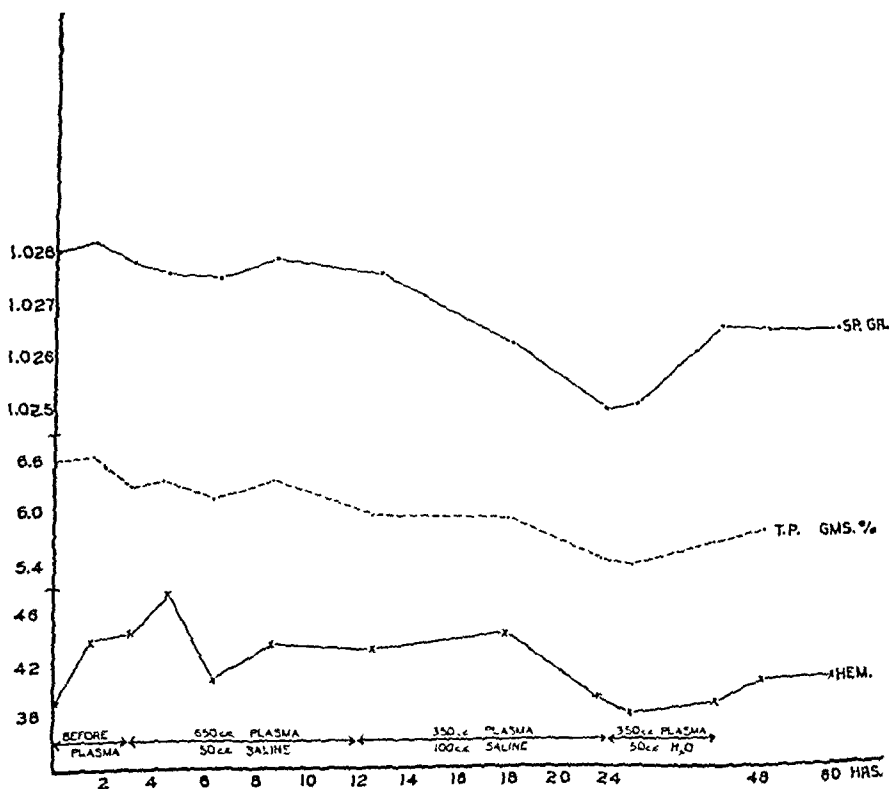


Fig. 1.—Graph of hematocrit and plasma levels after extensive burns in a 9-year-old child.

The second case illustrated is that of a 9-year-old girl who had received second- and third-degree burns of the trunk and arm involving about 30 per cent of the body surface (Fig. 4). The plasma specific gravity and protein concentration were maintained at a normal level by the injection of whole plasma and comparatively little saline. Her course during this period was uneventful, the blood pressure was maintained, temperature did not rise above  $38.5^{\circ}$  C., she tolerated fluids by mouth, and the urinary output was adequate. Although she was not as extensively burned as the first patient, the various observers agreed that she would have developed peripheral circulatory failure



without adequate therapy. The local burn was treated with sulfadiazine in triethanolamine.

Each burned patient must be evaluated as an individual problem. The red blood count and hemoglobin should be determined at frequent intervals. If facilities are available the red cell hematocrit, plasma specific gravity, and protein concentration yield valuable information in determining fluid therapy. In our experience the specific gravity and protein concentration have been found to decrease rather than increase during the first few hours before plasma is started. It is true that the specific gravity might have increased if treatment had been deferred sufficiently long to allow dehydration to develop. This early fall in specific gravity can be readily explained by the tremendous loss of fluid and proteins into the vesicles and into tissues beneath the burned area. The greatest loss of protein occurs during the first twenty-four hours, and whole plasma is usually necessary to compensate for this loss. There is relatively less protein lost during the second twenty-four hours, but in severe burns parenteral protein injections are still necessary. The hematocrit may fall below normal by the third or fourth day, necessitating whole blood transfusions. The necessity of determining the blood nonprotein nitrogen and chlorides should be stressed. No hard and fast rule of fluid therapy will be satisfactory in all patients, and only by careful attention to details can the patient be adequately treated.

#### CONCLUSIONS

1. The early recognition of shock and its therapy depend on a knowledge of the physiologic changes occurring in the failing circulation.
2. There is no single diagnostic criterion by which impending circulatory failure may be recognized and at the present time the diagnosis depends on a general evaluation of the patient. The inadequacy of single hematocrit and plasma specific gravity determinations has been stressed.
3. The plasma specific gravity may decrease rather than increase in the early stages of shock.
4. Adequate fluid therapy depends on the relative amounts of red cells, fluid, and protein which must be restored to the circulation.
5. Fluid therapy is most efficient when instituted before the patient develops the classical signs of shock.

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# STUDIES OF THE ARTERIAL OXYGEN SATURATION IN THE POSTOPERATIVE PERIOD AFTER PULMONARY RESECTION

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**A**NOXIA, or oxygen want in the tissues, has widespread detrimental effects that have been recognized for some time and many investigations on this subject have been published recently. Since one of the chief causes of anoxia is impairment in the oxygenation of the blood as it passes through the lung, one might expect to encounter anoxia following major thoracic operations. Clinically, however, oxygen want is often undetected, and the significance of anoxia of slight degree is not sufficiently appreciated. Little is known of the severity, frequency, and duration of oxygen want after pulmonary resection. In the present investigation several hundred determinations of the arterial oxygen saturation have been made in the postoperative period in order to obtain an accurate estimate of the degree of anoxia after the various types of major thoracic procedures, and these values have been compared in most instances with preoperative determinations. Special attention has been given to cases of pulmonary resection.

It should be emphasized that no attempt is made to evaluate all aspects of anoxia in thoracic surgery on the basis of the data here reported. We have studied the occurrence of lowering of the oxygen saturation of the arterial blood, that is anoxic anoxia, and we have some information about anemic anoxia from oxyhemoglobin capacity determinations, but to date we do not have accurate information concerning the importance of stagnant anoxia in thoracic surgery.

The recognition of lowering of the oxygen saturation of the arterial blood is of considerable clinical importance. The anoxia encountered after thoracic surgery usually can be corrected by the administration of an adequate concentration of oxygen by inhalation therapy. If untreated, the anoxia may be the forerunner of numerous postoperative complications.

## TECHNIQUE

A determination of the arterial oxygen saturation was usually done within the first few days after operation, and often on the first postoperative day. Additional determinations were made during the postoperative period, but none was made during the first few hours after operation when the effects of a general anesthesia were still present.

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followed in the postoperative period until a normal arterial oxygen saturation was found.

#### PNEUMONECTOMY

The results of the arterial oxygen saturation determinations after pneumonectomy are presented in Table I. In a few patients with a very satisfactory clinical course the arterial blood had a normal oxygen saturation within two to three days after removal of one lung. The majority of the patients, however, had slight reduction in arterial oxygen saturation for the first week after pneumonectomy. In no instance did the percentage saturation drop below 85 per cent at any time unless serious postoperative complications occurred.

In two cases there was a prolonged arterial oxygen unsaturation associated with a deviation in the position of the mediastinum. In one of these patients (E. B.) the clinical course was quite satisfactory but a large fluid accumulation on the operated side displaced the mediastinum into the normal side. Restitution of the mediastinum to a median position by the withdrawal of fluid resulted in a rapid return of the arterial oxygen saturation to a normal level. The other patient (D. M.) was a 62-year-old male with senile type of emphysema in both lungs and carcinoma of the left lung. Prior to the preoperative pneumothorax the arterial oxygen saturation was 90.7 per cent, which is almost normal for a man of his age. The arterial oxygen studies in the postoperative period were of great interest. The pneumonectomy was well tolerated as far as the surgical procedure was concerned. The arterial oxygen saturation dropped only slightly in the first few days after pneumonectomy. Although no surgical complications developed, the arterial oxygen saturation continued to drop gradually during the next three weeks. The pulmonary function was investigated and it was discovered that the residual air volume had reached the very high value of 70 per cent of the total lung volume. This finding indicated that because of the displacement of the mediastinum to the operated side the remaining lung was in a markedly overdistended state and as a result was not properly ventilated. In order to lessen the overdistention in the remaining lung a pneumothorax was induced on the operated side so that the mediastinum would be less deviated. With return of the mediastinum to approximately the preoperative position there was a rapid improvement in the arterial oxygen saturation associated with a decrease in the distention of the lung. The reason for the disturbance caused by the mediastinal displacement following pneumonectomy in this case was the pre-existing emphysema in the remaining lung. Following overdistention this already emphysematous lung could not adjust itself functionally as a normal remaining lung usually does after pneumonectomy.

#### LOBECTOMY

The results of the arterial oxygen determinations after lobectomy are presented in Table II. Following lobectomy the arterial oxygen satura-

In most instances the patients were receiving sedatives and narcotics during the period in which the studies of the arterial oxygen saturation were made, but rarely was the blood sample taken shortly after a narcotic was administered. Moreover, the doses of morphine employed were small. If the patient was receiving oxygen therapy, as was frequently the case in the early postoperative period, he was removed from the oxygen tent, or the oxygen by catheter or mask was discontinued for a period of at least thirty minutes, and usually over an hour, before the arterial blood was taken. It is recognized that even an hour after discontinuing oxygen therapy the blood may not have returned to its basic level of unsaturation, especially if the degree of anoxemia is severe. In some instances the taking of the blood was postponed for a day or so because it was considered inadvisable to discontinue the oxygen therapy even for one-half hour.

The arterial blood for analysis was obtained from the brachial artery under anaerobic conditions. The blood was drawn into pipettes within fifteen minutes of the time it was withdrawn from the artery. The oxygen content and oxygen capacity of the blood were immediately determined by the method of Van Slyke and Neill, and the per cent saturation calculated. All determinations were done in duplicate. In the method employed the normal range of saturation of the arterial blood with oxygen is 94 to 96 per cent except in older subjects in whom values down to 92 per cent may be regarded as normal.<sup>1</sup> We consider an arterial oxygen saturation of less than 90 per cent as indicating a clinically significant degree of anoxia. Less than 85 per cent saturation of the arterial blood indicates a relatively severe degree of anoxia.

The carbon dioxide content of the arterial blood was also determined, but since the results do not appear to be particularly significant the data on carbon dioxide are not presented.

#### MATERIAL

The oxygen saturation of the arterial blood was studied after a variety of thoracic surgical procedures, but particular attention was given to cases in which the patients had been subjected to pulmonary resection. A total of 17 patients was studied following pneumonectomy, and 13 of this group were followed until the arterial oxygen saturation returned to a normal level. The 4 remaining patients died in the postoperative period. Of the 17 pneumonectomy cases, 12 were total pneumonectomies, i.e., the lung was removed completely by hilar dissection, whereas in the remaining 5 cases a tourniquet was employed and a fragment of pulmonary tissue was left behind. In addition to these cases, there was one patient (M. K.) in whom all of the right lung except a small portion of the upper lobe was removed. This case will be discussed separately later.

A group of 21 patients was studied following lobectomy. In some of these cases a bilobectomy was done. In most instances the case was

	7/29/40	12 days	10.8	11.6	95.0	Uneventful postoperative course
S. J., aged 30; giant cyst and bronchiectasis of left lung. Subtotal pneumonectomy, 7/17/40						
W. J., aged 53; carcinoma of right middle lobe. Pneumonectomy, 5/8/40	4/25/40	Preoperative	18.0	18.6	97.7	Uneventful postoperative course
	5/9/40	1 day	15.9	17.6	91.6	
	5/14/40	6 days	14.7	15.9	93.5	
	5/28/40	20 days	11.0	15.0	91.6	
	7/3/40	8 weeks	15.2	16.0	95.9	
	10/1/40	5 months	17.2	17.9	97.2	
N. N., aged 56; tuberculosis of left lung with residual cavity after thoracoplasty. Subtotal pneumonectomy, 11/15/39	10/30/39	Preoperative	18.1	19.5	95.3	Marked dyspnea and paradoxical motion postoperatively in spite of normal arterial oxygen saturation in oxygen tent. Died on second postoperative day
		2 days	15.1*	16.4*	95.0	
L. R., aged 32; bronchiectasis of left lung. Pneumonectomy, 7/19/41	5/26/41	Preoperative	19.1	20.5	93.8	Uneventful postoperative course except for profuse bronchial secretions on second postoperative day
	7/21/41	2 days	15.0*	15.9	95.5*	
	7/22/41	3 days	13.2	14.0	95.2	
	12/15/41	5 months	14.5	15.7	93.4	
J. L., aged 42; bronchiectasis of left lung. Subtotal pneumonectomy, 11/8/39	10/12/39	Preoperative	16.1	17.5	91.7	Postoperative course satisfactory except for emphysema and bronchial fistula
	11/9/39	1 day	13.8	15.4	90.4	
	11/13/39	5 days	11.1	13.2	85.6	
	11/20/39	12 days	13.3	14.6	92.6	
	12/14/39	36 days	14.0	14.5	98.2	
	12/13/40	1 year	16.1	17.2	95.3	
A. M., aged 23; bronchiectasis of right lung with bronchiostenosis. Subtotal pneumonectomy, 5/8/41	5/6/41	Preoperative	17.1	17.9	96.1	General condition good postoperatively. Postoperative emphysema and amoebic dysentery
	5/7/41	1 day	15.2	15.8	97.7	
	5/13/41	7 days	14.0	15.2	93.1	
	7/8/41	63 days	14.3	14.9	97.2	
D. M., aged 62; carcinoma of left lung, bilateral fibrosis and emphysema. Pneumonectomy, 11/25/40	11/16/40	Preoperative	14.5	16.2	90.7	Postoperative condition quite satisfactory but arterial oxygen saturation continued to fall as mediastinal displacement toward operated side increased. Elevation of arterial oxygen saturation one month postoperatively coincident with retraction of mediastinum to mid-position by introduction of air
	11/25/40	2 days	15.1	17.5	88.6	
	11/30/40	7 days	14.1	16.0	89.1	
	12/4/40	11 days	13.6	16.0	86.1	
	12/10/40	17 days	13.5	16.2	84.1	
	12/17/40	24 days	13.1	15.4	85.9	
	12/26/40	33 days	15.2	16.8	91.4	
	1/20/41	58 days	15.8	17.8	90.4	
	7/28/41	8 months	14.2	15.8	90.6	

TABLE I  
PNEUMONECTOMY CASES

CASE	DATE	DURATION AFTER OPERATION	ARTERIAL OXYHEMOGLOBIN			REMARKS
			CONTENT (VOL. %)	CAPACITY (VOL. %)	SATURATION (%)	
R. B., aged 60; carcinoma of left lower lobe with atelectasis. Pneumonectomy, 10/21/39	10/17/39	Preoperative	14.3	14.9	96.9	Had bronchopneumonia 6 days postoperatively; gradual recovery. Atrial fibrillation present preoperatively and postoperatively
	10/24/39	3 days	14.6	15.5	95.1	
	10/27/39	6 days	12.9*	13.3*	98.1*	
	10/30/39	9 days	11.2	12.7	89.4	
	11/29/39	39 days	12.8	13.8	91.1	
	3/7/40	4½ months	18.7	19.4	97.1	
E. B., aged 31; carcinoma of left main bronchus with atelectasis of left lung. Pneumonectomy, 1/27/40	1/18/40	Preoperative	18.4	18.9	98.2	Pleural fluid on operated side displaced mediastinum to right during period of lowest arterial oxygen saturation; oxygen saturation became normal shortly after mediastinal deviation to unoperated side was corrected
	1/29/40	3 days	14.4	16.7	87.1	
	2/3/40	7 days	12.7	14.8	86.4	
	2/5/40	9 days	13.8	15.6	89.4	
	2/10/40	14 days	14.5	15.5	95.1	
	2/27/40	31 days	15.6	16.1	96.9	
T. G., aged 43; carcinoma of right main bronchus. Pneumonectomy, 9/28/39	9/21/39	Preoperative	18.4	19.5	95.0	Uneventful postoperative course
	9/29/39	1 day	17.0*	17.4*	98.6*	
	9/30/39	3 days	13.5	15.4	88.7	
	10/2/39	5 days	13.4	14.7	92.3	
	10/6/39	9 days	13.5	14.5	94.7	
	10/21/39	24 days	12.9	14.0	93.4	
J. H., aged 28; suppurative pneumonitis with multiple abscesses of right lung. Pneumonectomy, 5/23/40	2/29/40	Preoperative	13.6	15.0	91.4	Immediate postoperative condition satisfactory. Empyema drained on fifth postoperative day. Bronchus opened on eleventh postoperative day. Patient died on twelfth day
	5/1/40	Preoperative	15.2	16.2	94.4	
	5/25/40	2 days	10.2	10.7	97.3	
	5/29/40	6 days	12.3	12.9	96.8	
F. I., aged 46; old tuberculous stenosis of right main bronchus with bronchiectasis. Pneumonectomy, 5/19/41	1/23/41	Preoperative	19.7	20.5	97.0	Uneventful postoperative course
	5/21/41	2 days	15.6	17.6	89.5	
	6/3/41	15 days	13.6	14.6	93.6	



tion returned to a normal level somewhat more slowly than in the uncomplicated pneumonectomy cases. Most of the determinations made within a week of operation revealed some anoxic anoxia. In most of the cases in which the arterial oxygen saturation remained abnormally low for more than a week postoperatively some interference with pulmonary ventilation was present. In a few instances, however, the arterial oxygen saturation was low for a period of over a week in spite of excellent re-expansion of the remaining lobe on the operated side and in the absence of any postoperative complications. The explanation of this finding is apparently a temporary impairment in the correlation of ventilation and circulation in the remaining pulmonary tissue on the operated side. If, after lobectomy, difficulty is encountered in re-expansion of the remaining lobe on the operated side, several weeks may elapse before the arterial oxygen saturation reaches a normal level. In the case of G. M. the remaining lobe did not re-expand, but the arterial oxygen saturation nevertheless gradually became normal. If pleural fluid accumulates due to inadequate drainage after lobectomy, the remaining lobe may be compressed and oxygenation of the blood interfered with. If a pneumonic process develops in either lung, anoxia may result. The retention of bronchial secretion may lead to severe anoxia as well as atelectasis and pneumonic infiltration. Other factors are diminished respiratory movements and mediastinal displacement. Abnormalities of the remaining pulmonary tissue, especially emphysema and fibrosis, are of great importance.

A small amount of lung tissue which is poorly aerated, but still well perfused with blood, may significantly affect the arterial oxygen saturation. This is well illustrated by a case of bronchiectasis (M. K.) in which the right lower and middle lobes as well as a large part of the right upper lobe were removed. The remaining portion of the upper lobe re-expanded slowly. The arterial oxygen saturation remained between 86 and 90 per cent for six weeks after operation and did not reach a normal level until two months after operation. During most of the postoperative period there was no dyspnea or cyanosis but the patient complained of anorexia and headache which were improved by oxygen therapy. It seems probable that the remaining portion of the right upper lobe was perfused with blood from the pulmonary artery before adequate ventilation of these alveoli was restored. Had a total pneumonectomy been done instead, the arterial oxygen saturation would probably have reached a normal level much more rapidly. (Table I).

The effect of a bronchocutaneous fistula on the arterial oxygen saturation was studied in one case. When a large bronchial fistula develops after pneumonectomy, it is obvious that severe degrees of anoxia may result from interference with adequate ventilation of the remaining lung. We studied a case in which a moderate-sized fistula developed after lobectomy. The findings are shown in Table III.

TABLE 1—CONT'D

CASE	DATE	DURATION AFTER OPERATION	ARTERIAL OXYHEMOGLOBIN			REMARKS
			CONTENT (VOL. %)	CAPACITY (VOL. %)	SATURATION (%)	
W. R., aged 45; carcinoma of right lower lobe. Pneumectomy, 12/6/39	11/28/39 12/ 8/39	Preoperative 2 days	16.7 10.3 <sup>c</sup>	18.9 17.8 <sup>c</sup>	89.2 58.2 <sup>c</sup>	Postoperative pneumonia with profuse bronchial secretions. Died on second postoperative day. Last blood determination made shortly before death
M. S., aged 26; pulmonary tuberculosis with residual cavity and bronchocutaneous fistula following thoracoplasty. Pneumectomy, 6/24/40	9/22/39 6/29/40	Preoperative 5 days	15.3 18.6*	16.7 19.2*	92.7 97.7 <sup>c</sup>	Died post-operatively
G. T., aged 21; bronchiectasis of left lung, previous thoracoplasty. Pneumectomy, 7/15/41	3/ 8/41 7/23/41 9/12/41	Preoperative 8 days 2 months	16.0 11.0 13.9	17.6 12.2 14.5	91.6 91.6 96.8	Postoperative course satisfactory
V. W., aged 64; carcinoma of left upper lobe. Pneumectomy, 8/3/40	8/ 2/40 8/ 5/40 8/10/40 10/10/40 2/24/41	Preoperative 2 days 7 days 9 weeks 5½ months	15.8 14.5 12.7 14.8 18.4	17.2 15.5 13.8 15.8 19.8	93.1 94.7 92.8 95.1 93.8	Uneventful postoperative course
W. H., aged 47; carcinoma of left main bronchus with atelectasis of left lung. Pneumectomy, 1/15/40	1/17/40 1/23/40 4/ 5/41	2 days 8 days 15 months	17.5 18.6 18.7	18.4 20.3 19.8	91.8 92.9 95.6	Uneventful postoperative course
M. K., aged 36; suppurative pneumonitis of right lung. All of right lung removed except small portion of upper lobe, 8/12/39	8/19/39 9/ 8/39 9/13/39 9/18/39 10/ 2/39	7 days 27 days 32 days 37 days 7 weeks	10.6 11.6 14.6 16.8* 15.8	12.5 13.1 16.8 17.2* 17.0	86.0 89.8 88.1 99.2* 91.3	Headache and anorexia for several weeks postoperative. Residual portion of right lung re-expanded slowly

\*Patient receiving oxygen at time of determination.

\*Patient receiving oxygen at time of determination.

tion returned to a normal level somewhat more slowly than in the uncomplicated pneumonectomy cases. Most of the determinations made within a week of operation revealed some anoxic anoxia. In most of the cases in which the arterial oxygen saturation remained abnormally low for more than a week postoperatively some interference with pulmonary ventilation was present. In a few instances, however, the arterial oxygen saturation was low for a period of over a week in spite of excellent re-expansion of the remaining lobe on the operated side and in the absence of any postoperative complications. The explanation of this finding is apparently a temporary impairment in the correlation of ventilation and circulation in the remaining pulmonary tissue on the operated side. If, after lobectomy, difficulty is encountered in re-expansion of the remaining lobe on the operated side, several weeks may elapse before the arterial oxygen saturation reaches a normal level. In the case of G. M. the remaining lobe did not re-expand, but the arterial oxygen saturation nevertheless gradually became normal. If pleural fluid accumulates due to inadequate drainage after lobectomy, the remaining lobe may be compressed and oxygenation of the blood interfered with. If a pneumonic process develops in either lung, anoxia may result. The retention of bronchial secretion may lead to severe anoxia as well as atelectasis and pneumonic infiltration. Other factors are diminished respiratory movements and mediastinal displacement. Abnormalities of the remaining pulmonary tissue, especially emphysema and fibrosis, are of great importance.

A small amount of lung tissue which is poorly aerated, but still well perfused with blood, may significantly affect the arterial oxygen saturation. This is well illustrated by a case of bronchiectasis (M. K.) in which the right lower and middle lobes as well as a large part of the right upper lobe were removed. The remaining portion of the upper lobe re-expanded slowly. The arterial oxygen saturation remained between 86 and 90 per cent for six weeks after operation and did not reach a normal level until two months after operation. During most of the postoperative period there was no dyspnea or cyanosis but the patient complained of anorexia and headache which were improved by oxygen therapy. It seems probable that the remaining portion of the right upper lobe was perfused with blood from the pulmonary artery before adequate ventilation of these alveoli was restored. Had a total pneumonectomy been done instead, the arterial oxygen saturation would probably have reached a normal level much more rapidly. (Table I).

The effect of a bronchocutaneous fistula on the arterial oxygen saturation was studied in one case. When a large bronchial fistula develops after pneumonectomy, it is obvious that severe degrees of anoxia may result from interference with adequate ventilation of the remaining lung. We studied a case in which a moderate-sized fistula developed after lobectomy. The findings are shown in Table III.

TABLE II  
LOBECTOMY CASES

CASE	DATE	DURATION AFTER OPERATION	ARTERIAL OXYHEMOGLOBIN			REMARKS
			CONTENT (VOL. %)	CAPACITY (VOL. %)	SATURATION (%)	
K. B., aged 25; bilateral bronchiectasis. Right middle and lower lobe lobectomy, 5/2/40; left lower lobe lobectomy, 7/9/41	5/ 2/40	Preoperative	17.1	18.6	92.5	Slow convalescence complicated by empyema and bronchopleural fistula after each operation
	5/ 8/40	6 days	12.3	13.9	89.3	
	6/16/41	6 weeks	15.3	16.3	95.0	
	7/11/41	2 days	13.2	16.4	81.7	
	7/14/41	5 days	13.9	16.0	87.8	
C., aged 26; bronchiectasis, left lower lobe. Lobectomy, 5/23/40	5/28/40	5 days	12.3	14.3	86.8	Postoperative empyema and bronchopleural fistula but general condition good
	6/ 4/40	12 days	11.9	14.1	85.3	
	6/10/40	18 days	13.3	14.2	95.3	
	4/10/41	Preoperative	15.4	16.6	94.1	
	5/12/41	3 days	11.8	13.6	88.7	
F., aged 25; bronchiectasis, left lower lobe. Lobectomy, 11/14/39	11/14/39	Preoperative	16.5	18.6	89.3	Postoperative course complicated by empyema and bronchopleural fistula; later developed tuberculous pneumonia in left upper lobe
	11/22/39	8 days	11.1	15.6	71.8	
	11/27/39	13 days	11.6	14.2	82.9	
	12/ 5/39	21 days	9.7	14.2	68.5	
	12/11/39	27 days	11.0	14.3	77.4	
	12/18/39	34 days	12.3	13.1	94.9	
	12/19/39	33 days	8.6	13.2	65.6	
	12/29/39	45 days	12.7	14.6	87.6	
	1/15/40	2 months	13.4	15.2	89.2	
	3/13/40	4 months	12.8	13.9	93.3	
H., aged 38; chronic suppurative pneumonitis. Right upper and middle lobe lobectomy, 4/24/41	4/25/41	1 day	14.1	15.7	91.1	Uneventful postoperative course



TABLE II—CONT'D

CASE	DATE	DURATION AFTER OPERATION	ARTERIAL OXYHEMOGLOBIN			REMARKS
			CONTENT (VOL. %)	CAPACITY (VOL. %)	SATURATION (%)	
C. M., aged 37; bronchiectasis; right middle lobe and lower lobes; emphysema. Bilobec- tomy, 7/13/40	6/24/40	Preoperative	17.3	19.4	90.8	Died postoperatively of broncho- pneumonia and sepsis
	7/15/40	2 days	16.2*	17.2*	95.6*	
	8/1/40	19 days	12.8	14.2	91.4	
	8/3/40	21 days	13.8*	14.5*	96.5*	
C. P., aged 23; bronchiectasis, left lower lobe. Lobectomy, 6/5/41	6/6/41	1 day	16.9	20.3	83.9	Clinically uneventful postopera- tive course
	6/19/41	14 days	14.5	15.8	92.8	
L. R., aged 55; chronic pulmo- nary abscesses. Right upper and partial lower lobe lobec- tomy, 4/21/41	4/22/41	Preoperative	13.1	13.9	95.5	Poor expansion of remainder of right lung; postoperative em- pyema and pulmonary suppara- tion
	4/23/41	1 day	14.0	16.8	84.7	
	7/30/41	3 months	11.2	12.1	92.5	
R., aged 17; bronchiectasis, right upper lobe. Lobectomy, 5/29/41	5/21/41	Preoperative	18.8	20.2	96.4	Postoperative course quite satis- factory in spite of localized em- pyema and bronchial fistula
	6/2/41	4 days	11.5	12.8	91.5	
	6/19/41	21 days	15.3	16.1	96.1	
S., aged 38; bronchiectasis, right lower lobe. Lobectomy, 11/2/39	11/2/39	Preoperative	13.4	14.5	93.6	Poor re-expansion of upper lobe; had empyema with broncho- pneumonia
	11/4/39	2 days	13.9	15.0	94.2	
	11/7/39	5 days	12.0	13.7	88.8	
	11/13/39	11 days	10.4	12.1	87.6	
	11/20/39	18 days	12.4	13.7	91.8	
	12/13/39	6 weeks	13.2	14.0	95.6	
T., aged 26; bronchiectasis, left lower lobe; previous left thoracoplasty for tuberculous. Lobectomy, 6/26/41	1/12/40	10 weeks	14.5	15.7	93.2	Postoperative course satisfactory
	7/1/41	5 days	12.8	14.6	88.7	
	7/11/41	15 days	12.8	14.0	93.0	
V., aged 50; chronic pulmonary abscess. Partial left upper lobe lobectomy, 4/4/41	4/11/41	4 days	12.0	12.9	92.7	Postoperative course satisfactory except for small empyema

\*Patient receiving oxygen at time of determination.

\*Patient receiving oxygen at time of determination.

TABLE III

EFFECT OF BRONCHOCUTANEOUS FISTULA ON ARTERIAL OXYGEN SATURATION

FISTULA	ARTERIAL OXYGEN SATURATION (%)
Fistula open with patient breathing room air	87.2
Fistula closed with patient breathing room air for 45 min.	90.7
Fistula open with patient breathing 100 per cent oxygen for six min.	93.7
Fistula closed with patient breathing 100 per cent oxygen for 6 min.	96.7

## DISCUSSION

After surgical intervention in the thorax, anoxic anoxia is frequently present. Whereas the value of oxygen therapy in major thoracic surgery has been well established, no data have been available to aid in determining how long the anoxia persisted following operation. It is usually customary to administer oxygen for only a few days after operation unless the patient is obviously dyspneic or cyanotic. Yet our studies have shown that in some patients in whom no dyspnea or cyanosis was present a significant degree of anoxic anoxia persisted for weeks. When oxygen therapy was again instituted in such instances, marked clinical benefit was observed.

A comparison of the arterial oxygen saturation after pneumonectomy with the values obtained after lobectomy reveals the unexpected finding that the anoxic anoxia was apparently often more pronounced and lasted longer after lobectomy than after pneumonectomy in the absence of postoperative complications. The explanation of this finding lies in the fact that after uncomplicated total pneumonectomy all the blood flows through the opposite lung, which is well ventilated. Following lobectomy, however, the remaining lobe or lobes on the operated side are frequently poorly ventilated for a time postoperatively. Even though the roentgenogram may show good expansion of the remaining lobe immediately after operation, the actual ventilation of that lobe may be poor. Since a considerable amount of blood may be flowing through the pulmonary vessels of the poorly ventilated lobe, arterial oxygen unsaturation results. Pulmonary collapse because of failure of the lobe to re-expand, or collapse caused by compression from pleural fluid, was a frequent finding in those cases which showed marked or prolonged anoxic anoxia after lobectomy.

Following pneumonectomy there were only two cases without postoperative pneumonia or empyema in which the arterial oxygen saturation did not return to a nearly normal level by the end of the first week after operation. In both of these instances there was a close correlation between the arterial oxygen saturation and a change in the position of the mediastinum. In one patient (E. B.) the mediastinum was displaced toward the remaining good lung by a large fluid accumulation on the operated side. Following withdrawal of the excess pleural fluid and return of the mediastinum to a normal position there was a prompt return of the arterial oxygen saturation to normal. In the other patient

TABLE II--CONT'D

CASE	DATE	DURATION AFTER OPERATION	ARTERIAL OXYHEMOGLOBINS			REMARKS
			CONTENT (VOL. %)	CAPACITY (VOL. %)	SATURATION (%)	
C. M., aged 37; bronchiectasis; right middle lobe and lower lobes; emphysema. Bilobec- tomy, 7/13/40	6/24/40	Preoperative	17.5	19.4	90.8	Died postoperatively of broncho- pneumonia and sepsis
	7/15/40	2 days	16.2*	17.2*	95.6*	
	8/1/40	19 days	12.8	14.2	91.4	
	8/3/40	21 days	13.8*	14.5*	96.5*	
C. P., aged 23; bronchiectasis, left lower lobe. Lobectomy, 6/5/41	6/6/41	1 day	16.9	20.3	83.9	Clinically uneventful postopera- tive course
	6/19/41	14 days	14.5	15.8	92.8	
M. R., aged 55; chronic pulmo- nary abscesses. Right upper and partial lower lobe lobec- tomy, 4/21/41	4/22/41	Preoperative	13.1	13.9	95.5	Poor expansion of remainder of right lung; postoperative em- pyema and pulmonary suppara- tion
	4/23/41	1 day	14.0	16.8	81.7	
	7/30/41	3 months	11.2	12.1	92.5	
J. R., aged 17; bronchiectasis, right upper lobe. Lobectomy, 5/29/41	5/21/41	Preoperative	18.8	20.2	96.1	Postoperative course quite satis- factory in spite of localized em- pyema and bronchial fistula
	6/2/41	4 days	11.5	12.8	91.5	
	6/19/41	21 days	15.3	16.1	96.1	
J. S., aged 38; bronchiectasis, right lower lobe. Lobectomy, 11/2/39	11/2/39	Preoperative	13.4	14.5	93.6	Poor re-expansion of upper lobe; had empyema with broncho- pneumonia
	11/4/39	2 days	13.9	15.0	91.2	
	11/7/39	5 days	12.0	13.7	88.8	
	11/13/39	11 days	10.4	12.1	87.6	
	11/20/39	18 days	12.4	13.7	91.8	
	12/13/39	6 weeks	13.2	14.0	95.6	
	1/12/40	10 weeks	14.5	15.7	93.2	
B. T., aged 26; bronchiectasis, left lower lobe; previous left thoracoplasty for tuberculous. Lobectomy, 6/26/41	7/1/41	5 days	12.8	14.6	88.7	Postoperative course satisfactory
	7/11/41	15 days	12.8	14.0	93.0	
J. V., aged 50; chronic pulmonary abscess. Partial left upper lobe lobectomy, 4/4/41	4/11/41	4 days	12.0	12.9	92.7	Postoperative course satisfactory except for small empyema

\*Patient receiving oxygen at time of determination.



TABLE IV  
EXPLORATORY THORACOTOMY

CASE	TIME OF DETERMINATION	ARTERIAL OXYHEMOGLOBIN		
		CONTENT (VOL. %)	CAPACITY (VOL. %)	SATURATION (%)
R.B.	Preoperative	17.8	19.7	91.5
	4 days postoperative	15.6	17.2	91.7
H.G.	1 day postoperative	10.4	11.3	93.0
R.P.	Preoperative	15.3	17.0	91.0
	7 days postoperative	13.8	15.3	91.6
J.T.	Preoperative	16.9	18.4	92.7
	1 day postoperative	13.9	15.6	90.0
	5 days postoperative	13.0	14.7	89.5
R.Z.	Preoperative	16.1	17.3	93.4
	3 days postoperative	14.8	16.5	90.8

operative complications. Although most of the patients studied after thoracoplasty showed an appreciable drop in the per cent saturation of the arterial blood with oxygen, these findings do not give a true picture of the frequency of anoxia immediately following the thoracoplastic procedure. Not all of the patients subjected to thoracoplasty during a given period were studied but the investigation stressed rather the poor-risk group.

In order to determine whether the finding of postoperative anoxic anoxia was peculiar to thoracic surgery, a small group of patients who had undergone major abdominal surgery was studied as controls. In determinations of the arterial oxygen saturation of thirteen patients shortly after an abdominal operation, chiefly procedures in the upper abdomen, no instance of anoxic anoxia was found (Table V). None of these patients had any pulmonary complications but in some the diaphragm was elevated by abdominal distention. The patients were receiving morphine at the time the determinations were made.

TABLE V  
ABDOMINAL CASES

CASE	OPERATION	DAYS POSTOP- ERATIVE	ARTERIAL OXYHEMOGLOBIN		
			CONTENT (VOL. %)	CAPACITY (VOL. %)	SATURATION (%)
M.B.	Cholecystectomy	1	13.2	13.9	96.3
F.D.	Cholecystectomy	1	12.7	13.4	96.1
M.B.	Cholecystoduodenostomy	1	13.8	14.7	95.1
W.K.	Cholecystectomy	1	18.4	19.8	92.8
J.K.	Gastrectomy	4	12.7	13.6	94.3
J.M.	Appendectomy	2	19.6	20.9	94.4
J.S.	Gastrectomy	1	15.6	16.6	94.8
S.S.	Exploratory laparotomy	1	15.3	16.1	95.1
T.T.	Cholecystectomy	1	18.6	19.1	98.3
A.T.	Gastroenterostomy	1	13.0	14.1	93.8
J.T.	Laparotomy	1	14.7	15.7	94.6
E.W.	Cholecystectomy	1	11.4	12.2	94.4
M.H.	Exploratory laparotomy	2	12.9	14.1	93.0

(D. M.) the usual postpneumonectomy mediastinal deviation toward the operated side could not be tolerated because of the pulmonary emphysema present. Here again the arterial oxygen saturation returned to the preoperative level when the mediastinal displacement was lessened.

Longacre, Carter, and Quill<sup>2</sup> made an experimental study of some of the physiologic changes following total pneumonectomy in dogs. These authors did not study the animals in the early postoperative period but found little or no arterial oxygen unsaturation at rest two months after pneumonectomy. A severe exercise which had not caused anoxia before pneumonectomy resulted in marked arterial oxygen unsaturation after pneumonectomy. Longacre, Carter, and Quill quote Heuer and Andrus<sup>3</sup> as having noted in resting animals "a marked fall in the blood oxygen content up to the eleventh day, returning to normal by the twenty-fifth to thirtieth day." These determinations by Heuer and Andrus<sup>3</sup> were made on venous and not arterial blood. It is not stated whether the venous blood was mixed venous blood from the right heart or whether the blood was obtained from a peripheral vein, although this would influence the results. Studies of the arterial oxygen saturation in the early postoperative period after pneumonectomy in dogs would not be applicable to man. When pneumonectomy is performed in a dog, a contralateral pneumothorax results and therefore the expansion of the opposite lung may be altered to a considerable degree immediately after operation. There are practically no data to be found in the literature concerning the degree and duration of anoxic anoxia which may occur in the early postoperative period after major thoracic surgical procedures in man.

The effect which a bronchial fistula will have on the oxygen saturation of the arterial blood may vary with the size of the fistula. The effect of a bronchocutaneous fistula may be less marked than that of a bronchopleural fistula because of the possibility of more rebreathing with the latter. A large bronchial fistula may interfere seriously with adequate ventilation of the lungs. Touroff<sup>4</sup> has reported a case in which fatal anoxemia resulted from a large bronchopleural fistula following pneumonectomy. His patient became dyspneic and cyanotic whenever the opening to the large fistula was not occluded by a packing. No determinations of the arterial oxygen saturation were reported in that case.

The oxygen saturation of the arterial blood was determined in a small number of cases after thoracic exploration. The operative procedures were performed chiefly for pulmonary tumors which proved to be inoperable. All of the cases showed a slight reduction in the arterial oxygen with the saturation varying from 89.5 to 93.0 per cent (Table IV).

The arterial oxygen saturation was also studied in twenty-seven patients after thoracoplasty. A slight reduction in arterial oxygen saturation was often observed even in some good-risk patients with no post-

apy. In one patient (A. F.) restlessness, mental confusion, and hallucinations with muscular incoordination were observed during marked anoxia. The cause of the symptoms was suggested by the determination of the arterial oxygen saturation. Instead of waiting for such symptoms of anoxia to develop, however, it is preferable to make a determination of the arterial oxygen saturation routinely. By this means the presence of anoxic anoxia will be detected in its earliest stages and indicate that the administration of an atmosphere rich in oxygen may be beneficial.

#### SUMMARY AND CONCLUSIONS

Studies of arterial oxygen saturation have been made, before and after operation, in 17 cases that had pneumonectomy and in 21 cases that had lobectomies. From the data obtained the following conclusions were drawn.

1. Unrecognized anoxia is a common occurrence in thoracic surgery, and not infrequently is of major importance.

2. Following lobectomy there was frequently some degree of anoxia for a week. The remaining lobe on the operated side re-expanded poorly in two cases and the anoxia was more prolonged in these instances.

3. Following total pneumonectomy in the good-risk patient without complications, the oxygen saturation of the arterial blood returned to a normal level within a few days of operation.

4. Complications in the postoperative period after lobectomy and pneumonectomy frequently resulted in anoxia.

5. Significant anoxia was sometimes present in the absence of dyspnea and cyanosis. Symptoms such as headaches, restlessness, and mental confusion encountered in the postoperative period were in some instances due to anoxia.

6. If complications arise after pulmonary resection, prolonged oxygen therapy may be indicated.

7. Determinations of the oxygen saturation of the arterial blood after thoracic surgery may reveal unsuspected anoxia, sometimes of severe degree. Since the technique is simple, arterial oxygen determinations should become a part of the management of patients after pulmonary resection.

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It should be pointed out that a normal arterial oxygen saturation does not necessarily mean that oxygen therapy would be of no benefit. Although the saturation of the arterial blood may be within normal limits, the venous blood may have an abnormally low oxygen content and the tissues may not be supplied with adequate amounts of oxygen. The use of high oxygen concentrations may increase the oxygen content of the arterial blood above ordinary levels and thus be an aid in the treatment of stagnant anoxia.<sup>5</sup> Also, in spite of a normal arterial saturation, oxygen therapy may be indicated in stagnant anoxia for the purpose of reducing hyperventilation and decreasing whatever dyspnea is present.

Our present investigation has not included observations on the day of operation. The importance of avoiding anoxia during anesthesia and operation has received considerable attention recently. The importance of adequate ventilation and oxygenation during thoracic procedures cannot be overemphasized. Anoxia undoubtedly has been the main etiologic factor in many an instance of death during or shortly after a thoracic operation when the fatality was attributed to heart failure. Patients with pulmonary emphysema and fibrosis show the most marked disturbances in arterial oxygen saturation after thoracic surgery and even a relatively small intervention may cause considerable anoxia.

The effect of drugs which depress respiration must be considered in an evaluation of the causes of anoxia. During the early postoperative period the patients studied were receiving morphine and other sedatives. Generally the drugs were employed in small doses. The blood for analysis usually was not obtained in close relationship to the time when the sedative was administered. McClure and his co-workers<sup>6</sup> have reported anoxia after the administration of various sedatives and analgesics, but we do not believe that this is a significant factor in our results. The cases investigated after abdominal surgery were receiving similar doses of morphine at the time they were studied and did not show anoxic anoxia. Large doses of sedatives, however, may well be a factor in anoxia.

Determinations of the arterial oxygen saturation in the postoperative period after thoracic surgery have repeatedly demonstrated the inaccuracy of clinical criteria of anoxia. The unreliability of dyspnea and cyanosis as accurate signs of oxygen deficiency must be stressed. Severe anoxia may exist in the absence of cyanosis, especially if the patient is anemic. The importance of other signs and symptoms of anoxia, such as those seen at high altitudes, is frequently overlooked.

Our investigation permitted us to compare the presence of clinical signs or symptoms of anoxia with the arterial oxygen saturation. In a considerable number of cases there was no dyspnea in spite of anoxic anoxia. Cyanosis was often difficult to detect, sometimes because of pallor. A number of patients complained of headache and anorexia when the arterial oxygen saturation was below normal, and these symptoms, when caused by anoxia, were frequently relieved by oxygen ther-

apy. In one patient (A. F.) restlessness, mental confusion, and hallucinations with muscular incoordination were observed during marked anoxia. The cause of the symptoms was suggested by the determination of the arterial oxygen saturation. Instead of waiting for such symptoms of anoxia to develop, however, it is preferable to make a determination of the arterial oxygen saturation routinely. By this means the presence of anoxic anoxia will be detected in its earliest stages and indicate that the administration of an atmosphere rich in oxygen may be beneficial.

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Studies of arterial oxygen saturation have been made, before and after operation, in 17 cases that had pneumonectomy and in 21 cases that had lobectomies. From the data obtained the following conclusions were drawn.

1. Unrecognized anoxia is a common occurrence in thoracic surgery, and not infrequently is of major importance.

2. Following lobectomy there was frequently some degree of anoxia for a week. The remaining lobe on the operated side re-expanded poorly in two cases and the anoxia was more prolonged in these instances.

3. Following total pneumonectomy in the good-risk patient without complications, the oxygen saturation of the arterial blood returned to a normal level within a few days of operation.

4. Complications in the postoperative period after lobectomy and pneumonectomy frequently resulted in anoxia.

5. Significant anoxia was sometimes present in the absence of dyspnea and cyanosis. Symptoms such as headaches, restlessness, and mental confusion encountered in the postoperative period were in some instances due to anoxia.

6. If complications arise after pulmonary resection, prolonged oxygen therapy may be indicated.

7. Determinations of the oxygen saturation of the arterial blood after thoracic surgery may reveal unsuspected anoxia, sometimes of severe degree. Since the technique is simple, arterial oxygen determinations should become a part of the management of patients after pulmonary resection.

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## THE EFFECT OF ATROPINE ON GASTRIC SECRETION DURING THE NIGHT

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THERE have always been differences of opinion concerning the secretion of gastric juice during the interdigestive period. Spallanzani (1783) and Brown (1876) postulated that the secretion of gastric juice is continuous. Beaumont (1847) observed that the gastric juice was never found free in the unstimulated stomach of Alexis St. Martin. As early as 1895, Schnele studied the secretion and motility of the normal human stomach by means of a catheter left in situ. Pavlov (1910) and his pupils believed that, in the absence of secretory stimuli such as food, acting from the mouth cavity, stomach, or upper part of the small intestine and when certain "psychic influences" are also absent, the peptic glands remain in a state of rest under which condition no gastric juice is secreted.

Rehfuss, beginning in 1914, determined the previous conception of the fasting stomach to be erroneous by obtaining amounts of 30 to 120 c.c. of fasting secretion from healthy medical students. Carlson (1916) found that, in the absence of food or psychic factors, there was a continuous secretion of the gastric glands varying from 2 to 50 c.c. an hour with an average content of 40 c.c. of fluid in the fasting stomach. He observed that this continuous or "hunger secretion" had a uniformly lower acidity than the appetite juice. Crohn and Reiss (1917) believed that an "after secretion" might persist for many hours postprandial but they considered it a manifestation of pathologic hypersecretion; they were unable to duplicate the work of Rehfuss in normal individuals. Rehfuss and Hawk (1921) inferred that the gastric residua which they obtained were due to a constant secretion of the gastric glands which they believed to be continuously active. They found during the interdigestive period that the secretory rate, the free acidity, and the total acidity were all reduced. Lim (1924) considered the continuous secretion as the "basal secretion" of the stomach to which the subsequent enhanced activity of the glands, as a result of controlled stimulation, must be related. Chalfen (1928) and Henning and Norpoth (1933) reported that normal subjects did not have an acid secretion during the night in contradistinction to the secretion of a juice of high acid value by patients suffering from peptic ulcer. Winkelstein (1935) confirmed this work when he found that nine out of twenty normal patients showed no free acid secretion during the night, the remainder having very low values with a composite peak

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of 12° at eleven o'clock. He reported that the quantity of secretion seldom exceeded 15 c.c. during the whole night, whereas patients with peptic ulcer averaged high volume and acid values.

Hellebrandt and co-workers (1936) contrasted the diurnal and nocturnal responses of the same normal subjects. They found that, in general, the acidity of the gastric juice spontaneously liberated during sleep at night was higher than that produced during the day and postulated that if the stomach has the ability to liberate spontaneously a juice of high acid value, its nocturnal responsiveness exceeds that of the day.

Sandweiss (1941), in studying gastric secretion at night in both normal individuals and peptic ulcer patients, reports that he obtained secretory volumes in both groups much higher than previously reported. He found the volume of secretion significantly higher in ulcer patients although the concentration of free acid was about the same in both groups.

Many theories have been postulated to explain the mechanism of interdigestive gastric secretion. It has been attributed to the mechanical irritation of the tube or a result of psychic influences producing a secretion via the vagus nerve. Carlson believed that the products of the autodigestion of the mucin and proteins in the gastric juice yielded gastric secretagogues which act as chemical stimuli for a slow continuous gastric secretion. However, Hellebrandt has pointed out that continuous aspiration affords minimal opportunity for this to take place. The whole problem was reviewed by Babkin (1932), who advanced the view that continuous gastric secretion is always due to the action of normal or abnormal stimuli among which he listed conditioned reflexes, the swallowing of saliva and regurgitation into the stomach of duodenal juices, food residuum in the stomach, food masses in the intestine, skin disease or infection, and the presence of gastric gases. Hellebrandt, in emphasizing the cyclic nature of the production of acid, postulates that gastric secretion, like gastric motility, is augmented during sleep at night, the secretory and motor mechanisms of the stomach being similarly governed.

The importance of thoroughly comprehending the nature of the interdigestive gastric secretion is readily realized when the role of acid in the production of peptic ulcer is considered. The occurrence of ulcer only in those individuals whose stomachs secrete free hydrochloric acid; the hypersecretion of gastric juice in ulcer patients (particularly duodenal ulcer); the occurrence of ulcer only in those parts of the gastrointestinal tract exposed to the action of gastric juice; the occurrence of ulcer in Meckel's diverticulum adjacent to patches of ectopic fundus mucosa; the absence of recurrent ulcer in patients exhibiting achlorhydria after gastrectomy; the success of medical management of ulcer when based on the principle of neutralization of the free acid; experimental ulcer production when gastric secretion impinges on a mucosa unprotected

by alkaline duodenal secretion, and the experimental production of ulcer in laboratory animals after the injection of histamine in beeswax—all these occurrences contribute to accumulated evidence that acid gastric juice is the *sine qua non* of ulcer. Thus, it is believed highly probable that during the interdigestive phase the acid gastric juice, undiluted by other secretions and unmixed with diluting, adsorbing, and neutralizing foodstuffs may be harmful to the mucous membranes. Whether the hypersecretion and hyperchlorhydria during the night are cause or effect, it is fair to suspect that the acid gastric juice is responsible for the initiation of the lesion, for its extension, and for its chronicity.

There have been many attempts to control gastric secretion by the administration of pharmacologic products. Atropine and related compounds, because of their effect on the parasympathetic nervous system, have been extensively used. The regulatory activity of the vagus nerve on gastric acid secretion is an established fact but the influence of the splanchnics is still open to question. Bickel (1925) believed that the sympathetic nervous system had the major role in the production of enzymes by the gastric glands whereas the parasympathetic nervous system played a secondary part, influencing chiefly the secretion of water and acid. Baxter (1934) has shown that the sympathetic nervous system has some relation to the secretion of mucoid fluid by the gastric mucosa. However, it has never been definitely demonstrated that the sympathetic nerves directly influence the activity of the peptic or parietal cells.

The site of action of atropine is usually considered to be on the post-ganglionic nerve endings in the cells or neurocellular substance but the subject is not clearly settled. Gray and Atkinson have suggested that, since atropine does have some effect on the secretory response to histamine, it must act on the cell as well. Ivy advanced the suggestion that atropine may prevent the formation of the secretory hormone in the stomach.

Since atropine depresses the parasympathetics, one would expect it to depress or completely inhibit the primary or cephalic phase of gastric secretion, which is a reflex transmitted to the stomach via the vagus nerve. In laboratory animals it has been found that the secretion of appetite juice may be abolished by atropine. In human beings, Rehfuess found that  $\frac{1}{50}$  gr. atropine, given hypodermically, reduced this secretion but did not abolish it. The intestinal phase of gastric secretion is, according to Ivy, mediated by the vagi and in laboratory animals is diminished or abolished by large doses of atropine. There have been no reports of the effect of atropine upon this phase in human subjects.

What atropine does to the gastric or chemical phase, however, is not clear. The vagi also seem to be concerned in the mechanism of this phase for Orbeli (1906) has demonstrated that after their section this secretion is diminished. Klein (1933) has shown that in dogs atropine



can abolish the secretion due to chemical stimuli in the stomach in transplanted pouches deprived of all peripheral nerve supply and subject only to humoral influences. In man, however, some (Pokras and Michelson) believe that this phase cannot be suppressed although Bastedo states that doses large enough to cause toxic reactions may inconstantly bring about a distinct reduction in the amount of secretion and acid titer. It should be borne in mind, however, that the gastric phase is given its start by the chemical substances formed from food by the action of psychic juice; thus, it is possible that if the appetite juice is diminished, the chemical juice will be developed more slowly.

Many other investigators have extensively studied the effect of atropine on gastric secretion. All who have observed its effect in animals agree that secretion is checked in all of its normal phases. Keeton (1933) found that in the dog the first effect of atropine is to decrease total quantity of both the gastric secretion and the pepsin content whereas the acid concentration is not decreased until a sufficient amount of atropine has been given to reduce the total quantity of secretion to an amount approximately 20 to 50 per cent of its original volume. Atkinson and Ivy (1938) confirmed these results, obtaining a volume reduction of 50 per cent in the response of the Pavlov pouch secretion to histamine with a diminution of 66 per cent in the total acid output as measured in milligrams. Bastedo suggested that these results could only be expected with the large doses of atropine that can be given the experimental animal.

However, there exist wide differences of opinion concerning the effect of atropine in man. Porter (1932) observed that the height reached by the free acidity was not affected by atropine but that the volume was definitely decreased, the reduction varying from 40 to 60 per cent. Keefer and Bloomfield (1926) and Atkinson and Ivy (1936) obtained similar results, the former reporting a marked diminution in the total quantity of secretion as well as a reduction in the acidity without parallelism in the degree of reduction of each. Atkinson and Ivy, studying the effect of atropine and its derivatives on the gastric secretion of ulcer patients, concluded that there was no effect on the height of the titratable acidity but that the volume of secretion was diminished in comparison with the control. To obtain this effect, they found it necessary to administer doses of atropine large enough to produce untoward side reactions.

Lockwood and Chamberlin (1922) found that maximal chemical dosages of atropine depressed both the free and total gastric acidity about 30 per cent. Bolton (1923) and Roberts (1925) confirmed this observation; all believed that the attendant relaxation of the pyloric sphincter associated with the regurgitation of the alkaline intestinal fluid, as indicated by the earlier appearance of bile in the samples and by the sudden or gradual rise of the inorganic chloride curve, allowed neutralization to occur earlier or more frequently.

Kalk and Siebert (1927), Polland (1930), and Klumpp and Bowie (1933) reported that the volume of secretion was reduced after atropine but that the free acid values were higher. Polland attributed the rise of titratable acidity to the relatively slight inhibitory effect of atropine upon the total output of acid with a consequent increase in the amount of acid per cubic centimeter of gastric content.

Crohn (1918) was unable to produce any reduction in gastric acidity by the use of atropine. Winkelstein (1933) obtained equivocal results. Palmer (1933) and Bastedo (1936) observed that atropine diminished the volume and acidity of gastric secretion but only in quantities sufficient to produce other unpleasant physiologic effects. The effect on gastric secretion was short lived while the toxic manifestations persisted for longer periods. In doses permissible for continuous therapy, they found that belladonna and atropine were practically without effect on the secretory and motor functions of the stomach. Bastedo emphasized that frequently the reduction in the volume of secretion is associated with a much smaller proportionate reduction in the total acid secreted resulting in a more strongly acid solution than normal with consequent increased irritant action. Doses large enough to reduce acid secretion were also found to reduce the secretion of protective mucin.

There are many others who have reported the reduction of gastric acidity by the administration of physiologic doses of atropine. Riegel (1899) found that atropine caused a decrease of free and total acid after a test meal of one liter of milk. Moore and Kilroe (1910) reported a reduction averaging  $13.6^{\circ}$  for free acid and  $13.10^{\circ}$  for total acid after the administration of belladonna by mouth. Mathieu and Roux (1914) considered atropine the most useful drug at their disposal for cases of hypersecretion. Schmidt (1914) believed that atropine diminished the secretion of the gastric glands and advocated its use in hyperacidity. Bennett (1921) found consistent diminution in gastric acidity after the administration of therapeutic doses of oral atropine. Schuff (1900), Bergman (1913), Chiari (1915), Hernando (1923), Kilterman (1925), Roll (1926), and Loeper and Fau (1933) may be listed among the many others who agree that atropine is effective in reducing gastric acidity.

The question as to why so many divergent results have been reported concerning the effect of atropine on gastric secretion has frequently been raised. Atshuler (1928) attempted to reconcile contradictory observations on the basis that the action of the drug depends upon what phase of activity the cells are in when the stimulus reaches them. He believes that the same drug acting on the same cell might at one time result in stimulation and at another in inhibition. However, it is probable that most of the inconsistencies are due to differences in atropine dosage and method of administration, different types of stimuli used to induce secretion (test meals, alcohol, histamine), duration of test period, time relationships relative to the administration of atropine, and

differences in criteria used for determining inhibition of secretion. The reason for the difference in atropine action between man and dog is unknown. Klein postulates that one cause may be that more of the humoral stimuli act directly on the cell in man; in this case atropine would be relatively less effectual.

### METHOD

Observations were made upon fifty University Hospital patients who presented no evidence of gastrointestinal disease other than chronic cholecystitis<sup>15</sup> and recurrent appendicitis in the interval phase.<sup>11</sup> In addition, fifteen patients with active duodenal ulcers were studied.

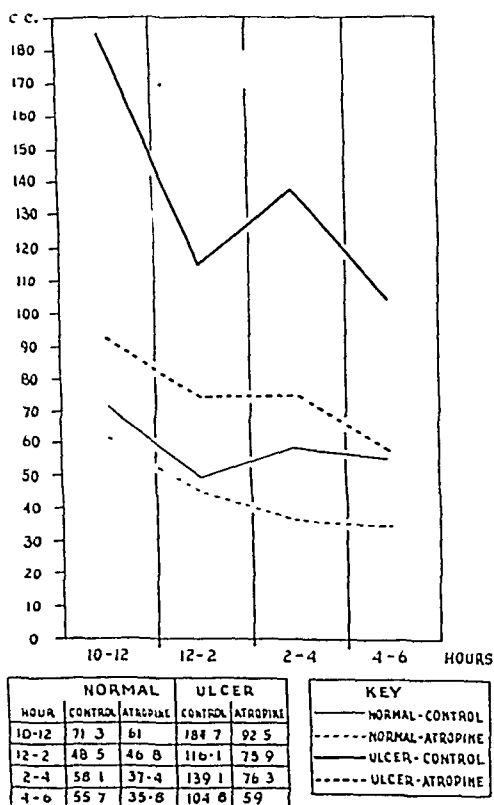


Fig. 1—Graph showing volumes of gastric juice secreted at night by fifty normal and fifteen ulcer patients (average values).

The average age of the group selected as normal was 41.4 years, the youngest patient being 16 years, the eldest 75 years. Thirty were female, twenty male. In the ulcer group, thirteen were male, two female. The average age was 45.6 years with the youngest 29 years, the eldest 64 years.

The method of study of the patients in each group was identical. Each patient was studied on two successive nights, the first night serving

as a control and atropine being given on the second. The usual hospital meals were served on each of the days preceding the test, the five o'clock dinner consisting of soup, meat, potato, vegetable, and dessert. Duodenal tubes were inserted through the nose into the stomach at seven o'clock, no lubricant being used and suction siphonage instituted

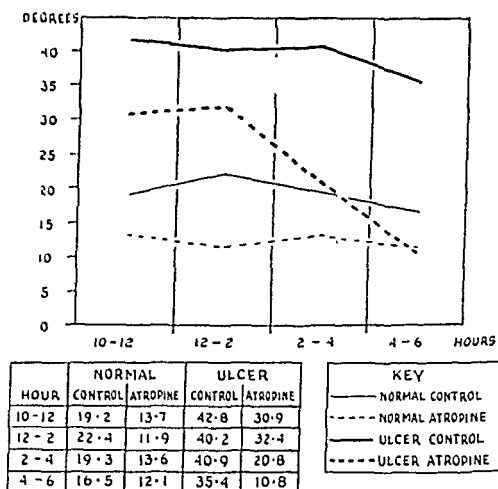


Fig. 2.—Graph showing free acidity of gastric juice secreted at night by fifty normal and fifteen ulcer patients (average values).

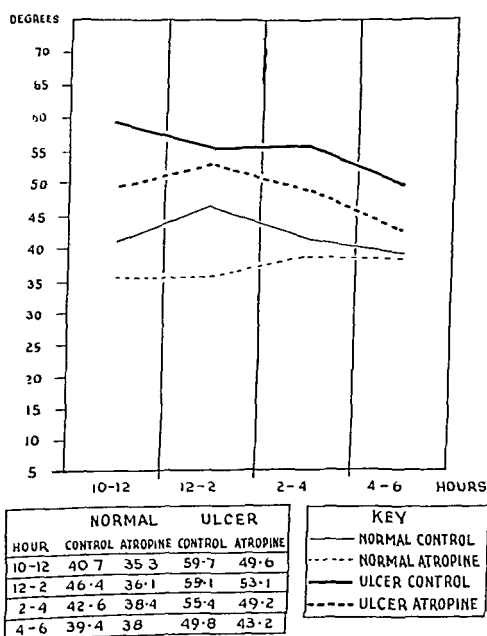


Fig. 3.—Graph of total acidity of gastric juice secreted at night by fifty normal and fifteen ulcer patients (average values).

directly. At nine o'clock, 2 gr. sodium luminal were given hypodermically; this was repeated in five hours if the patient was still awake. No fluids were allowed after nine o'clock. No attempt was made to aspirate the salivary secretion.

At ten o'clock the returns from the suction were discarded, following which collection was made of the gastric secretion at intervals of two hours during the night. On the second night, the procedure was identical except for the administration of  $\frac{1}{4}$  gr. atropine sulfate dissolved in 120 cc of tap water by proctoclysis at 10 P.M., 1 A.M., and 4 A.M., using a continuous drip adjusted to a rate of four drops a minute.

The volumes of each of the two hourly returns were measured and the free and total acidity determined using Toepfer's solution and phenolphthalein as indicators. No accurate notations were made regarding the presence of food particles, bile, blood, etc. in the samples.

## RESULTS

The results are graphically recorded in Figs. 1, 2 and 3. The normal group presented a mean secretory rate of 29.3 cc. per hour in contrast to the average of 68 cc. per hour in the control ulcer series. With the use of atropine there was a mean decrease in the volume of secretion, free and total acidity as shown in Table I.

TABLE I

	NORMAL GROUP	ULCER GROUP
Volume	53 cc. (22.6%)	60 cc. (44.2%)
Free acid	5° (34%)	16° (40.4%)
Total acid	5° (12.4%)	6° (11.1%)

TABLE II

EFFECT OF ATROPINE ON THE NIGHTLY SECRETION OF GASTRIC JUICE STUDY OF 50 NORMAL AND 15 ULCER PATIENTS

	NORMAL 50 CASES			ULCER 15 CASES		
	VOLUME	FREE ACID	TOTAL ACID	VOLUME	FREE ACID	TOTAL ACID
Significant decrease (>20%)	25	24	20	12	10	8
No change (±20%)	14	11	15	1	3	4
Significant increase (>20%)	12	12	15	2	2	3

Table II represents an evaluation of the effect of atropine upon each individual studied. The net change for the period of 10 P.M. to 6 A.M., following the administration of atropine, in volume, free and total acidity of gastric juice secreted was calculated for each patient; a significant increase or decrease was considered as a variation from the control of more than 20 per cent.

Of the twenty-four cases in the normal series showing a significant decrease in the amount of free acid after atropine administration,

eighteen had no free acid in two or more of the two-hour periods and nine had no free acid in all four of the two-hour periods. Five patients in the ulcer group were achlorhydric in all specimens after the administration of atropine.

The only untoward side action to atropine noted was a dryness of the mucous membranes of the nose and throat of which the majority of the patients complained. Tachycardia exceeding 100 was present on only five occasions. No patient exhibited cerebral symptoms from the administration of the drug.

#### SUMMARY

1. The nightly gastric secretion of fifty normal and fifteen ulcer patients was studied on each of two successive nights, the first night serving as a control, with atropine being given by proctoclysis the second night.

2. In the control period, mean values indicate that the secretory rate, volume of secretion, free and total acidity are higher for the ulcer group. Atropine diminished the volume of secretion as well as the free and total acidity in both the normal and ulcer series. The decrease in these values was more pronounced in the ulcer group.

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# ENDOMETRIOSIS: CLINICAL AND THERAPEUTIC CONSIDERATIONS

WITH A REPORT OF 120 PRIVATE CASES

R. L. SANDERS, M.D., MEMPHIS, TENN.

ENDOMETRIOSIS, after more than twenty years of fairly intensive investigation, still holds the unabated interest of physicians and surgeons, for several reasons. Its etiology remains largely a matter of speculation, its pathologic and clinical manifestations continue to defy recognition, and the proper methods of its treatment are still disputed. Further, the condition is far more prevalent than the profession in general yet realizes. Chiefly responsible for this fact, no doubt, is its common association with adenomyosis and other pelvic diseases; the surgeon is easily deceived into attributing the patient's symptoms to one or more of these disorders and overlooking entirely the possibility of endometriosis.

Believing that a fuller appreciation of the true incidence of endometriosis can be gained, and that some of the problems involved can best be clarified by reports of individual experiences and studies of selected cases, I will discuss the clinical and therapeutic features of the condition as I and others have observed them, and will follow this with a critical review of my own cases treated within recent years.

Opinion regarding the mode of origin of endometriosis is divided chiefly between two theories: one, that of Sampson,<sup>9</sup> that the masses develop from bits of müllerian mucosa deposited on the peritoneum by retrograde menstrual flow; that they either remain superficial or invade and contract the underlying structure; and that, after invading the ovary, they enlarge and give rise to a cyst, which ruptures and in turn disperses other implants over the pelvic structures. According to the second theory, suggested by Ivanoff,<sup>3</sup> the process develops by metaplasia of celomic epithelium. Still another possibility was advanced by Cullen<sup>2</sup>: that the endometrial tumors grow from embryonic rests of müllerian tissue. In any event, it is generally believed that the basic factor is a glandular imbalance which results in overactivity of the hormones, and, further, that this influence often continues in the ectopic endometrium, causing it to enlarge and recede with each menstrual period.

Just when this hormonal activity begins to incite the pathologic process is likewise a matter of conjecture. Some authors believe it begins with the onset of menstruation, or soon thereafter, and progresses slowly over a period of years. This may be true of cases in which the



uterus is not involved; it is questionable, however, whether it applies to those wherein benign uterine disease is associated, although the latter also is believed to be activated by glandular hyperfunction. It has been our observation, and that of others as well, that adenomyosis usually develops in older women.

The reason for the later appearance of tumors of the uterus may lie in the structure of the organ, which may possibly prevent their early manifestation. Yet, this does not fully explain the difference. Dreyfuss,<sup>3</sup> among others, has suggested that multiparity may be one factor in uterine tumors, the sterility index being lower than normal in the lower age group. Meigs<sup>7</sup> is of the opinion that the appearance of endometriosis, on the other hand, may be favorably influenced by late marriage and contraception, in that hormone function is unrelieved by the physiologic rest afforded by pregnancy. Could the difference be one of origin? The theory of metaplasia of celomic epithelium might best apply to endometriosis without uterine disease, especially since patients so affected fall in the younger age groups.

This thought leads to a consideration of the role of sterility in endometriosis. Since both sterility and endometriosis are evidence of glandular imbalance, it is conceivable that they are coincident features of the same disturbance rather than, as some authors believe, that sterility is an active agent in the disease process. This would seem to be true whether the endometriosis develops in a nullipara, the sterility in this case being primary, or whether symptoms present themselves following one or more pregnancies, the sterility then being secondary.

The frequent association of retroversion with endometriosis has given rise to the opinion that this condition may also be a contributing influence. I am convinced, however, that, with few exceptions, the retroversion in these cases is caused by puckering and consequent shortening of the uterosacral ligaments by the implants, or by fixation of the uterus to the sigmoid by adhesions incident to implants between these two structures.

*Pathology.*—In the majority of cases, external endometriosis involves one or both ovaries, and the pelvic peritoneum as well. In the ovary, it is usually present in the familiar chocolate cyst, though fragments of endometrial tissue are occasionally found in hemorrhagic and other types of ovarian cysts. Outside the ovary, the implants may be widespread over the pelvic floor and on the pelvic wall, or may be scattered at only a few points. The most common site is the posterior wall of the uterus, the uterosacral ligaments and the sigmoid also being involved. Generally, in such cases, the uterus is drawn backward and is attached to the sigmoid, and the whole constitutes a fixed mass. Often, extensive deposits are distributed along the sigmoid or rectum. Other common locations are the bladder fold of the peritoneum and anterior wall of the uterus and cervix, rectovaginal septum, and broad ligament. Rarely, endometrial tissue is found in the inguinal region, in the

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R. L. SANDERS, M.D., MEMPHIS, TENN.

ENDOMETRIOSIS, after more than twenty years of fairly intensive investigation, still holds the unabated interest of physicians and surgeons, for several reasons. Its etiology remains largely a matter of speculation, its pathologic and clinical manifestations continue to defy recognition, and the proper methods of its treatment are still disputed. Further, the condition is far more prevalent than the profession in general yet realizes. Chiefly responsible for this fact, no doubt, is its common association with adenomyosis and other pelvic diseases; the surgeon is easily deceived into attributing the patient's symptoms to one or more of these disorders and overlooking entirely the possibility of endometriosis.

Believing that a fuller appreciation of the true incidence of endometriosis can be gained, and that some of the problems involved can best be clarified by reports of individual experiences and studies of selected cases, I will discuss the clinical and therapeutic features of the condition as I and others have observed them, and will follow this with a critical review of my own cases treated within recent years.

Opinion regarding the mode of origin of endometriosis is divided chiefly between two theories: one, that of Sampson,<sup>9</sup> that the masses develop from bits of müllerian mucosa deposited on the peritoneum by retrograde menstrual flow; that they either remain superficial or invade and contract the underlying structure; and that, after invading the ovary, they enlarge and give rise to a cyst, which ruptures and in turn disperses other implants over the pelvic structures. According to the second theory, suggested by Ivanoff,<sup>5</sup> the process develops by metaplasia of celomic epithelium. Still another possibility was advanced by Cullen<sup>2</sup>: that the endometrial tumors grow from embryonic rests of müllerian tissue. In any event, it is generally believed that the basic factor is a glandular imbalance which results in overactivity of the hormones, and, further, that this influence often continues in the ectopic endometrium, causing it to enlarge and recede with each menstrual period.

Just when this hormonal activity begins to incite the pathologic process is likewise a matter of conjecture. Some authors believe it begins with the onset of menstruation, or soon thereafter, and progresses slowly over a period of years. This may be true of cases in which the

only clue to the nature of the disease. Indeed, the patient may have no difficulty whatever except at the menstrual period. An illustration of this fact is found in tumors of the broad ligament or abdominal wall, which manifest themselves solely by local tenderness and swelling at menstruation.

Primary invasion of the sigmoid or rectum probably presents the most serious of the diagnostic problems associated with endometriosis. Although deposits are frequently found in these areas as a part of a *general pelvic distribution*, they seldom involve the colon wall to such an extent as to give rise to symptoms, and a primary endometrioma is even more rare.

Signs of obstruction, the palpation of a mass posterior to the uterus, and the proctoscopic finding of a puckered area in the lumen of the bowel without an appreciable reaction in the surrounding tissues are fairly definite proof of the endometrial nature of the growth. The roentgenographic demonstration of a lesion is useful, but cannot be relied upon for a differential diagnosis.

Occasionally, however, without any definite warning, one is confronted at operation with a growth in the sigmoid or rectum which simulates cancer and is entirely unaccompanied by other areas of endometriosis. Unless one is familiar with the clinical characteristics of such lesions, the patient is likely to be subjected to a colon resection on the diagnosis of malignancy. A case is reported herein, in which this was done, several years ago. The most significant point in the diagnosis is the fact that endometriomas of the colon, as of other regions, are manifested by the usual menstrual symptoms.

*Treatment.*—The treatment of endometriosis is, in my opinion, entirely surgical. If the implants are extensive, involving both ovaries, all the pelvic organs should be extirpated. When only one ovary is affected, however, and all the peritoneal implants are removable, the good ovary may be left undisturbed. In young patients who complain of dysmenorrhea, a presacral resection may be performed in conjunction with a conservative operation, to prevent recurrence of the pain in the event of persistent endometriosis. The principal question in any case is not the patient's age, but the relief of symptoms and prevention of further damage and perhaps serious consequences, by interruption of the disease. If this can be accomplished without completely destroying ovarian function, well and good; if not, the radical operation should be carried out. The only exceptions are encountered in those patients at or near the menopause, whose symptoms are mild and in whom the disease may be expected to subside with the cessation of menstruation. In all other cases, the process is likely to cause trouble so long as ovarian function continues.

When the sigmoid or rectum is invaded, it may be advisable to resect the growth by an elliptical incision, in addition to oophorectomy. Partial resection of the colon is unnecessary; according to our experience, the growth will regress following removal of the ovaries.

perineum, on the small bowel, appendix, and abdominal wall, and in the omentum, umbilicus, lungs, and laparotomy scars.

Whether deposited primarily through the tubes or secondarily from perforated cysts, as Sampson believes, or whatever their origin, the implants tend to incite an inflammatory reaction and adhesions in the adjacent structures; thus, at operation, one may observe an acute, widespread peritonitis, all the pelvic organs being bound together in an almost impenetrable mass of adhesions. This process, incidentally, explains many inflammatory conditions of the pelvis for which formerly no cause could be assigned.

*Symptoms.*—The cardinal features of peritoneal endometriosis are menstrual irregularity and pelvic pain. The menstrual disorder is usually a menorrhagia or metrorrhagia, though some patients have only a spotting between periods, or even amenorrhea. The pelvic pain may be general, or localized to one side or another, or it may be referred to the back or down the thighs. Referred pain is especially significant, indicating, usually, a penetrating lesion or one which has incited an inflammatory reaction. Again, the pain may be severe, or may be described as a drawing sensation, or merely a soreness, tenderness, or discomfort in the pelvis. The intensity of the pain is believed to be governed by the function of the implants under hormonal influence. The more severe pain may be acute in onset, resembling that of acute appendicitis or an acute intestinal obstruction. The milder types are usually chronic, covering a period of months or years.

Not all patients, however, have either menstrual disturbance or pain. Rather, many of them complain of symptoms referable to the gastrointestinal or urinary tract, a vaginal discharge, nervousness, loss of appetite and weight, headache, and dyspareunia. A few come to the physician solely because of an abdominal mass. Others seek examination because of sterility. When such conditions are accompanied by abnormal menstruation and low abdominal pain, they afford additional evidence of endometriosis; alone, however, they may present a confusing and entirely misleading picture which cannot be clarified except by a thorough pelvic examination and more often than not, not even then. Especially is this true of younger women in whom the process is not well advanced.

*Diagnosis.*—The most reliable diagnostic measure is rectovaginal examination. By this means, fixed, painful, nodular masses in the uterosacral ligaments, in the cul-de-sac, or on the rectovaginal shelf may be readily detected, and when present, may be regarded, practically without doubt, as endometriomas. Similarly, retroversion and uterine tumors and ovarian cysts may also be palpated. If adhesions are extensive, however, the different organs may be indistinguishable, and individual areas of endometriosis impossible of delineation.

Especially significant in the diagnosis is the fact that symptoms are exaggerated during menstruation. Not infrequently, this feature is the

- Abdominal endometriosis, 5 (omentum, 3; cecum 1; appendix, 1; abdominal wall, 1)  
 Associated benign disease of uterus and cervix, 84  
 Associated cancer of uterus, 1  
 Associated cysts of ovaries other than endometrial, 14  
 Associated hydrosalpinx, 5  
 Displacements of uterus, 41 (retroversion, 39; prolapse, 2)  
 Sterility, 24 (23 per cent of 104 married patients)

As shown above, the endometrial cysts of the ovary were bilateral in 50 cases and unilateral in 33. In 12, the endometriosis was confined to the ovaries alone, whereas in 23 it was limited to the peritoneum and other extraovarian structures. Peritoneal implants and cysts of the ovaries, endometrial and otherwise, were found together in 81 cases. Benign disease of the uterus and cervix was associated in 83 cases, and cancer of the uterus in 1, the 84 cases representing 70 per cent of the total. Other surgeons have reported a similar incidence of uterine and cervical disease.

The relative incidence of endometriosis and disease of the uterus and cervix in the different age groups is shown in Table I.

TABLE I

INCIDENCE OF ENDOMETRIOSIS AND DISEASE OF UTERUS IN 120 PATIENTS IN DIFFERENT AGE GROUPS

	17 TO 20		20 TO 30		30 TO 40		40 TO 50		50 AND OVER	
	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT
Endometriosis alone (36 patients)	2	6	12	33	17	47	5	14	0	
Endometriosis and uterine disease (84 patients)	0		7	8	28	33	44	53	5	6
Total	2		19		45		49		5	

The average age of those with external endometriosis alone was 31.5 years, and of the second group, 41 years. This finding conforms to that of other surgeons, that uterine disease develops later than endometriosis.

Five patients had previously had one ovary and tube removed, 23 had had an operation on the cervix or vagina or a curettage, 3 a shortening of the ligaments, and one a presacral neurectomy for dysmenorrhea.

The series was also reviewed with the idea of determining whether any relationship might exist between the ages of the patients and the extent and severity of the disease. The endometrial process was regarded as mild in 41 cases and severe in 79. The number and ages of the patients with each type are shown in Table II.

Contrary to the experience of some authors, we did not find more severe or more extensive endometriosis in the younger patients. Approximately 80 per cent of those with the severe type, and 75 per cent

The greatest difficulty in making a decision as to the best course to pursue is encountered when these patients present themselves for examination because of sterility. The slight possibility of subsequent pregnancy, despite preservation of the reproductive function, hardly compensates for the dangers of erring on the side of conservatism. Thirty-one per cent of a group of patients reported by Dreyfuss<sup>3</sup> were sterile, and Counseller<sup>1</sup> found an absolute sterility of 32.1 per cent of patients at the Mayo Clinic.

The use of radium or x-ray therapy in endometriosis seems hardly justifiable. In the first place, the risk to life is not a serious consideration in the choice of treatment, since the mortality from surgery is negligible. In the second place, there is almost invariably some associated disease which irradiation cannot relieve, and, in this event, radium is likely to give rise to infection and pelvic abscess. Or, if a sufficient amount of irradiation is given to destroy ovarian function, the uterus will be materially damaged. Further, the climacteric, with all its unpleasant manifestations, follows irradiation just as surely as it follows extirpation of the ovaries, yet all the diseased structures remain in the pelvis. Certainly, irradiation should never be given until the abdomen is opened, and then not until the presence of endometriosis is definitely proved by thorough exploration. An exact diagnosis is impossible without laparotomy.

I have collected a series of 120 cases of pelvic endometriosis discovered at operation within the past six years. These have been taken from our private clinic records and are therefore believed to give a fairly accurate picture of the incidence of the disease among surgical patients. The study does not include those with hemorrhagic or other types of ovarian cysts than the chocolate endometrial variety. Nor does it include adenomyosis unless associated with endometriosis, since a pathologic study was made of relatively few uterine specimens removed during this period. Moreover, in view of the more serious surgical considerations involved, our interest has been primarily in endometriosis.

The 120 cases of this series were encountered in a total of approximately 700 laparotomies for gynecologic diseases carried out during the same period, representing an incidence of 17 per cent. One hundred and four of the patients were married. The ages ranged from 17 to 53 years, the average being 38 years. Two were under 20 years; 19 between 20 and 30; 45 between 30 and 40; 49 between 40 and 50; and 5 beyond 50. Of the entire group, chocolate endometrial cysts of the ovaries were found in 83 (69 per cent) patients, and cysts of questionable endometrial origin and of other types were found in an additional 14. The endometrial process involved the peritoneum and other extra-ovarian structures in 106 (89 per cent). The distribution of the lesions and associated pathology is shown here.

Ovarian endometriosis, 83 (bilateral, 50; unilateral, 33)  
Peritoneal endometriosis, 106

Abdominal endometriosis, 5 (omentum, 3, cecum 1; appendix, 1, abdominal wall, 1)  
 Associated benign disease of uterus and cervix, 84  
 Associated cancer of uterus, 1  
 Associated cysts of ovaries other than endometrial, 14  
 Associated hydrosalpinx, 5  
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	UP TO 20		20 TO 30		30 TO 40		40 TO 50		50 AND OVER	
	NUM BEL.	PER CENT	NUM BEL.	PER CENT	NUM BEL.	PER CENT	NUM BEL.	PER CENT	NUM BEL.	PER CENT
Endometriosis alone (16 patients)	2	6	12	33	17	47	5	14	0	
Endometriosis and uterine disease (84 patients)	0		7	8	28	33	44	51	5	6
Total	2		19		45		49		5	

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TABLE II

INCIDENCE OF MILD AND SEVERE ENDOMETRIOSIS IN 120 PATIENTS IN DIFFERENT AGE GROUPS

AGE GROUP (YEARS)	MILD ENDOMETRIOSIS		SEVERE ENDOMETRIOSIS	
	PATIENTS		PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Up to 30	8	20	13	16.5
30 to 40	14	34	31	39
40 to 50	17	41	32	40.5
50 and over	2	5	3	4
Total	41		79	

with the mild type were between 30 and 50 years of age. Twenty per cent of those with a mild endometriosis and 16.5 per cent with the severe degree were under 30 years of age.

The uterus was retroverted in 39 patients and prolapsed in 2. Of the total of 41, uterine disease was associated with the endometriosis in 20 cases, and in 21 endometriosis was present alone. As shown in Table I, 36 patients of the entire series had endometriosis without disease of the uterus; the incidence of 21 retroversions in the group of 36 therefore represents 58.3 per cent. The 20 patients with retroversion and both endometriosis and uterine disease constituted 24 per cent of the total number of 84 patients in whom the combined conditions were found. Thus, comparatively, retroversion was present with endometriosis alone in more than twice as many cases as retroversion with both endometriosis and disease of the uterus and cervix. Of the group of 21, there were 15 under 35 years of age, whereas in the group of 20, only 2 were under that age.

Twenty-eight of the 104 patients who were married had never borne children; 4 of this number, however, reported having one or more miscarriages. Nine of the 28 had retroversion, the uterus being bound in malposition by adhesions in every case. The only 4 of the 28 who might possibly have borne children, having one good ovary and an otherwise normal uterus, were among those with retroversion.

The symptoms as described by the total number of 120 patients were classified as follows:

- Dysmenorrhea, backache, referred pain, 45
- Pelvic pain and discomfort, 41
- Menstrual disorders, 59 (Menorrhagia, 53; irregularity, 2; menopause, 4)
- Miscellaneous, 61 (Gastrointestinal disturbance, cystitis, headache, nervousness, vaginal discharge, abdominal mass, dyspareunia)
- Indefinite or no symptoms, 3

Counseller<sup>1</sup> has observed that menorrhagia usually is associated with chocolate cysts, and dysmenorrhea and referred pain with uterine and peritoneal endometriosis. We were unable to establish a connection between menorrhagia and dysmenorrhea or referred pain, respectively,



and the pathologic condition as it involved the ovaries, uterus, and peritoneum. Forty of the 55 patients with menorrhagia and irregular menstruation had some disease of the uterus, and 42 had peritoneal endometriosis. Three had peritoneal endometriosis alone, neither the uterus nor ovaries being affected. In only one patient with menorrhagia was the endometriosis limited to the ovaries; on the other hand, 14 who complained of menorrhagia had neither chocolate cysts nor any other disease of the ovaries.

Of the 45 patients with dysmenorrhea, 34 had cysts of the ovaries, 28 had some disease of the uterus, and the peritoneal and other structures were involved in the endometrial process in 41. Eleven patients with dysmenorrhea also had retroversion, and 10 of this number had pelvic endometriosis.

Forty-one patients described a low abdominal pain, pelvic discomfort, or pressure sensation which was apparently unrelated to menstruation. Thirty gave a history of gastrointestinal symptoms, 3 of this number having no other complaint. The sigmoid was involved in 10 of the 30, but could not be held entirely responsible for the symptoms because of associated disease of the appendix. Symptoms referable to the bladder were reported by 9 patients, 13 complained of a vaginal discharge, 11 of headaches, 3 of dyspareunia, and 11 were aware of a pelvic mass.

TABLE III

DURATION OF SYMPTOMS IN 120 ENDOMETRIOSIS PATIENTS IN DIFFERENT AGE GROUPS

AGE GROUP (YE.)	UP TO 1 YR.	1 TO 2 YRS.	3 OR MORE YRS.	NO SYMPTOMS	UNKNOWN
Up to 30	12	4	3	0	0
30 to 40	21	5	16	1	1
40 to 50	22	15	9	2	3
50 and over	1	2	2	0	0
Total	57	26	30	3	4

In Table III is shown the duration of symptoms as reported by the patients in each age group.

The duration of symptoms was recorded in 116 cases. Three patients had no symptoms. Of the 116, 83 (70 per cent) had had symptoms less than three years, 17 (20 per cent) of the 83 being under 30 years of age, 26 (31 per cent) between 30 and 40, 37 (45 per cent) between 40 and 50, and 3 (4 per cent) beyond 50. It is noteworthy that some of the younger patients had suffered for years, whereas some of the older ones had had symptoms for only a few days or few weeks.

A study of the duration of symptoms in the mild and severe types, respectively, revealed nothing important. As would be expected, in the majority of cases, the symptoms were of longer duration in the severe type. Some of the milder cases, however, including those wherein no endometrial deposits were found outside the ovary had produced symptoms over a long period of time, while a number wherein the deposits

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was a married woman, aged 31 years, who had a total hysterectomy and unilateral salpingo-oophorectomy. The patient whose symptoms have returned was a young lady, aged 25 years, who had only a mild peritoneal endometriosis without disease of the ovaries or uterus; surgery was limited to shortening of the ligaments. These four cases represent



D Sturm

Fig. 1B—Specimen open, showing interior

22 per cent of the 19 patients whose ovarian function was not completely destroyed. Since the 4 patients from whom we have not heard had bilateral oophorectomies, this is probably a fairly accurate estimate of the results in the entire group. At the last report, none of the patients who had the more conservative operations had borne children.

TABLE IV  
RESULTS OF OPERATION IN 120 CASES OF ENDOMETRIOSIS

		NUMB. PER CENT
Mortality	0	
Complete relief	112	93.3
Partial relief	3	2.5
No relief	1	0.8
No report	4	3.3

were widespread were first manifested by 'an acute attack of a few hours' to a few days' duration.

A preoperative diagnosis of *endometriosis* was made in 29 (24 per cent) of the cases. The operations performed were as follows: Bilateral salpingo-oophorectomy, 97 (in 4, a portion of the ovary was transplanted); unilateral salpingo-oophorectomy, 20 (including 5 patients who previously had a salpingo-oophorectomy); hysterectomy, 109; shortening of ligaments, 6; presacral nerve resection, 1. Ovarian function could be preserved in 9 of the 11 whose uterus was undisturbed.

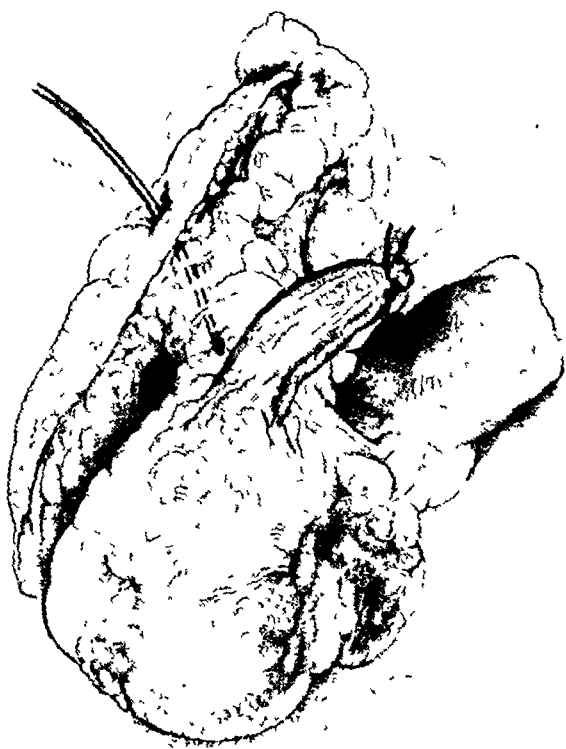


Fig. 1A.—Inguinal endometrioma of round ligament, 2 by 3 inches, with sinus through which patient menstruated each month.

I have never had a patient die from operation for *endometriosis*. Four of the present group have not been heard from since leaving the hospital. Of the other 116, 112 were completely relieved by the operation, 3 were only partially relieved, and 1 has had a recurrence of the dysmenorrhea from which she suffered prior to operation. One of the patients who was only partially relieved was a girl, aged 19 years, for whom a presacral neurectomy was performed, the pelvic organs being undisturbed because of her age and the mild degree of *endometriosis*. Another was a young unmarried woman, aged 28 years, who had a subtotal hysterectomy and unilateral salpingo-oophorectomy. The third

On examination, a hard, nodular, inflammatory mass with a sinus opening was found in the groin and extending into the labium. The tissues over the mass were darker than normal. The cervix was in good condition, and the uterus was of normal size and movable, but retroverted. No mass could be found in the pelvis. The tentative diagnosis was endometriosis, with possibly incarceration of the tube in the hernial sac.

At operation, a firm tumor, approximately 2 by 3 inches in diameter, was discovered in the region of the groin and labium over the inguinal canal. From the outer side of the tumor, passing into the groin, was a sinus through which the patient had been menstruating. The mass was fastened deep in the fascia, making its liberation difficult. When freed from the labium and groin tissues, a hernial sac was discovered leading out from the inguinal ring. None of the intestine or omen-

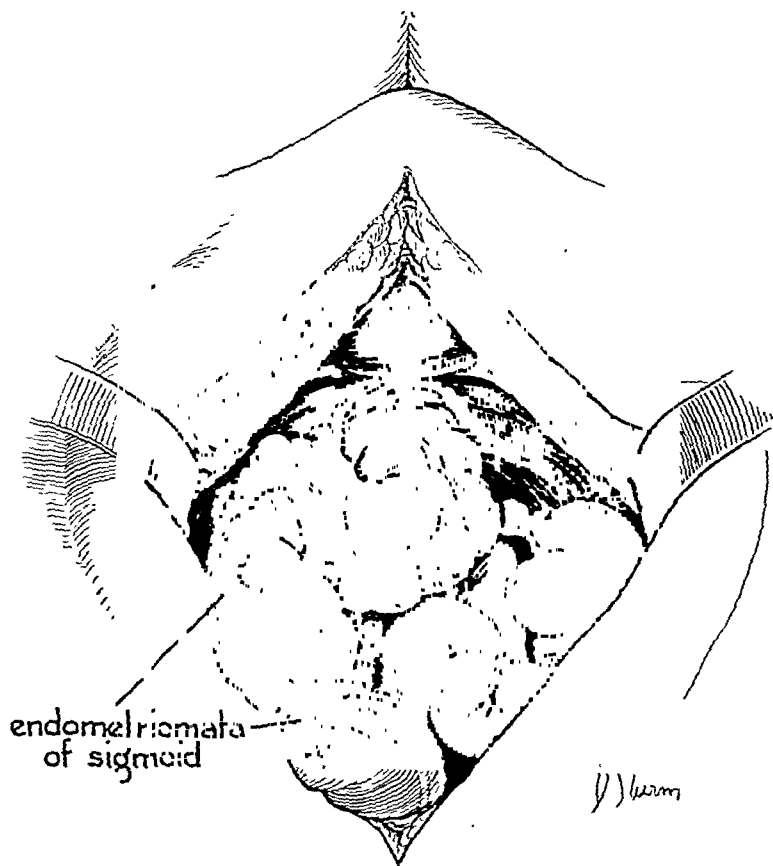


Fig. 2.—Two distinct endometriomas of the sigmoid of which the larger, distal lesion produced considerable obstruction. The intervening 2 inches of colon was entirely normal. The sigmoid was resected on clinical diagnosis of carcinoma; microscopic sections proved the lesions to be endometriomas. Mikulicz operation done and recovery followed.

tum was contained in the sac. The round ligament, which came out beneath the sac, was quite large and the tumor was attached to its extreme end over the pubic region.

The involved portion of the ligament was removed with the tumor, the remaining portion being fixed to the fascia to support the uterus. The hernial sac which had

A large number of these patients have received theelin for control of menopausal symptoms. We were at first uncertain as to the effect of the drug and feared that it might possibly promote a recurrence or continuance of the endometrial process. Accordingly, we have examined a number of patients with this in mind. We have found no evidence that theelin reactivates the disease, nor does it appear to have any influence on the recession of growths left in the pelvis. We believe, therefore, that theelin should be given as a replacement therapy to make these patients comfortable.

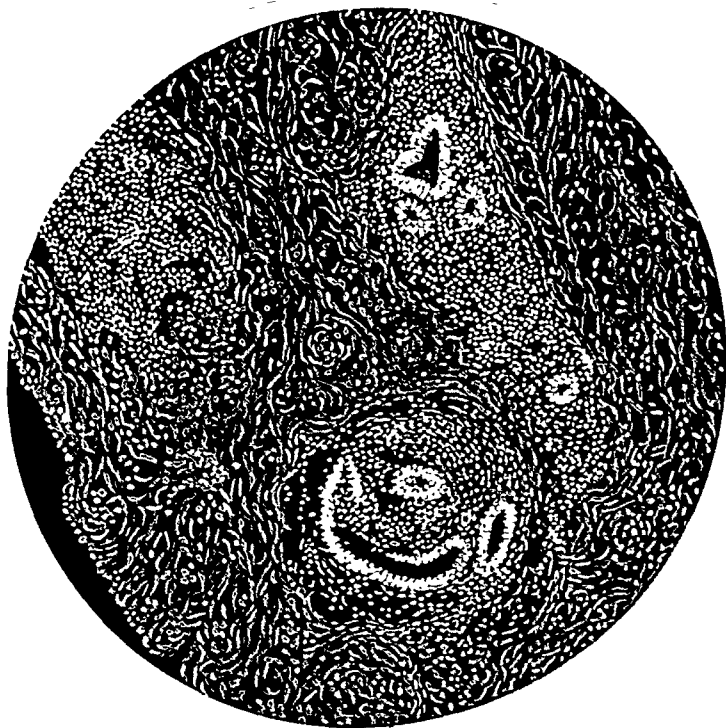


Fig. 1C.—Microscopic section of specimen, showing endometrial glands.

Four of the most unusual cases of this series are reported in detail. The first is that of a patient who had an endometrioma of the round ligament, from which menstrual blood passed through a small sinus opening into the groin.

CASE 1.—Mrs. J. R. S., a multipara, aged 41 years, came for examination because of a hernia which had been present for twelve years. Four months prior to her visit, she began passing blood and purulent material through the hernial mass at menstruation. This phenomenon was associated with severe pain, both local and referred down the thigh, but never with a rise of temperature.

Aside from the pelvis, the examination revealed nothing abnormal. The uterus was of normal size, in good position, and movable. There was a large, tender Bartholin cyst, and the cervix was moderately lacerated, cystic, and eroded. In the cul de sac, a tender mass the size of an English walnut could be palpated, and in the left uterosacral ligament there was a thickened, tender area. The diagnosis was pelvic endometriosis.

The cyst was incised and drained, and when healing was complete, operation for the pelvic condition was carried out.

The cervix was coned and the cystic sac excised. When the abdomen was opened, the uterus, ovaries, and tubes were found to be normal. The large, tender area previously detected proved to be an indurated napkinring tumor of the sigmoid, with fixation to the uterosacral ligament and posterior uterocervical juncture. The entire circumference of the sigmoid was puckered into a fold and the growth presented every appearance of cancer. A thorough search revealed no endometrial implants on any of the pelvic structures. A few inches higher on the sigmoid, however, there was another small puckered area. This was excised, and a diagnosis of endometrioma was reported on frozen section. It was then believed that the larger tumor was also an endometrioma. Accordingly, the uterus, tubes, and ovaries were removed, the sigmoid dropped back into its normal position, and the abdomen closed. Recovery followed without incident.

On request, the patient returned six weeks postoperatively for a check up and roentgenographic examination of the colon. The pelvis was in good condition and she had no complaint other than the usual menopausal symptoms. The bowel function was normal. Proctoscopic examination was negative. A roentgenogram revealed some spasticity of the sigmoid, but no evidence of an encircling lesion.

When last heard from, in January, 1941, five months after operation, the patient stated that she was still taking theelin, but otherwise felt like a new person.

The last case is one of multiple endometrioma of the omentum associated with red degeneration of the uterus. I had never before or have never since observed a combination of these two conditions.

CASE 4—Mrs. J. H. H., aged 46 years, nullipara, came for examination in January, 1938, because of pain in the lower abdomen and down the thighs. The pain had begun one week earlier, had been sufficiently severe to keep her in bed, and had been accompanied by a rise of temperature. She had also lost several pounds in weight since the onset of the pain. Until two months previously, her menstrual periods had always been regular, since that time, she had menstruated more often and more freely than usual.

Palpation of the abdomen revealed a large pelvic mass, irregular in outline, and extending almost to the umbilicus. On pelvic examination, the mass was found to be firm and partially fixed. The cervix was normal. The preoperative diagnosis was fibroid tumor.

Exploration revealed two large fibroids posteriorly and several smaller tumors on the anterior wall of the uterus. There was a considerable amount of red discoloration of the serous covering of the uterus, and the surrounding tissues were waterlogged and inflammatory. When the uterus was removed and opened, an area of red degeneration approximately 4 inches in diameter was found in the center of the largest fibroid. This accounted for the edema and inflammatory reaction of the tissues and explained the patient's fever. Both ovaries contained simple cysts and were removed with the tubes, the latter being normal.

There were no endometrial implants on the pelvic structures. In the omentum, however, which was thicker than normal, were two firm areas, not unlike metastasizing carcinoma. Both were excised and were reported by the pathologist to be endometriomas.

The patient's postoperative course was smooth and she has since been entirely well.

led into the tumor was divided, transfixed and ligated, and the stump was Kocherized. Finger exploration of the pelvis through the opening revealed no indication of any other disease process. The hernia was repaired and the abdomen closed. The pathologic diagnosis of the tumor mass was inguinal endometrioma involving the round ligament.

The patient has had no further difficulty since her dismissal from the hospital, four years ago.

The patient in the following case had two endometriomas of the sigmoid, but no other evidence of the disease. The sigmoid was resected in the belief that the condition was malignant. This operation was performed ten years ago.

CASE 2—Mrs. J. L. L., nullipara, was first seen in March, 1931, at the age of 39 years. She complained of intestinal disturbance, and stated that at each menstrual period her symptoms became more severe and were accompanied by the passage of blood and mucus from the bowel. All the details of the examination at that time are not now available, our record, however, shows that a mass was palpated in the cul de sac. Since I had not previously encountered a case of endometrioma of the sigmoid, the exploration was carried out under a diagnosis of cancer or diverticulitis.

When the abdomen was opened, a firm, nodular, contracting lesion was discovered in the mid portion of the sigmoid, and a second, similar lesion one inch distally. In view of the finding of two distinct masses, it was believed that they were diverticula and were undergoing malignant change. There was no evidence of metastases in the glands or other organs. The uterus, tubes, and ovaries were practically normal and were not disturbed.

A three stage resection was done. At the second stage, when the sigmoid was removed, a search was made for endometrial implants in the rectovaginal septum and elsewhere in the pelvis, though none were found. On microscopic section of the growths, a diagnosis of adenomyomas of the endometrial implant type was reported. The mucosa was not involved.

The patient was next seen in May, 1936, when she returned for a general check up. She had had no menstrual pain nor any digestive symptoms since the operation, five years earlier. The function of the colon had remained good, and she felt entirely well. No further masses could be detected in the pelvis.

Eighteen months later, in October, 1937, she consulted us again because of fatigue and pelvic discomfort. She was then 46 years old and was menstruating only at intervals of six months. Pelvic examination disclosed a tender, firm area in the cul de sac, which was regarded as an endometrioma. The uterus was of normal size. Since the patient was passing through the menopause, surgery was considered unnecessary.

At her last examination, in December, 1940, the patient's symptoms had subsided and menstruation had entirely ceased. The mass could still be palpated in the cul de sac, though it had diminished in size since the preceding examination.

The following case is also one of endometriosis of the sigmoid without involvement of other structures. Profiting by my experience in the previous case, I removed the ovaries and uterus, but left the sigmoid intact.

CASE 3—Mrs. W. D. M., multipara, aged 36 years, consulted us in July, 1940. She was referred for treatment of a recurrent Bartholin cyst which had first appeared nine years earlier. In addition to this complaint, she gave a history of increasing dysmenorrhea, pelvic soreness, and metrorrhagia over a period of three years.



In the Methodist Hospital, during 1938, 1939, and five months of 1940, a diagnosis of endometriosis was made in 38 of 1170 pelvic operations, or 3.8 per cent. A complete report could be obtained from the Baptist Memorial Hospital only for the year 1939: endometriosis was recognized in 27, or 4.7 per cent of 576 cases in which the pelvic cavity was opened. Also of interest is the fact that at the John Gaston Hospital, which is a teaching institution devoted almost entirely to charity patients, a diagnosis of endometriosis was made in 12 of a total of 929 pelvic laparotomies performed during 1939 and 1940, representing an incidence of 1.3 per cent. In similar reviews, Long and Strecker<sup>6</sup> found a diagnosis of endometriosis in 0.96 per cent of pelvic laparotomies at the St. Anthony Hospital, a charity institution in Oklahoma City, and Pumphrey<sup>8</sup> encountered an incidence of 2.23 per cent in pelvic operations at the Miami Valley Hospital, also a general hospital, in Dayton, Ohio.

Compared with Meigs<sup>7</sup> reported incidence of 32.2 per cent of cases of endometriosis in abdominal gynecologic operations in private practice, and even with my finding of endometriosis in 17 per cent of pelvic laparotomies, these figures speak for themselves. Certainly, they call in forceful terms for a better understanding and a wider recognition of this disease.

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Idem: Peritoneal Endometriosis Due to Menstrual Dissemination of Endometrial Tissue into the Peritoneal Cavity, *Am. J. Obst. & Gynec.* 14: 422, 1927.  
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The last two of the foregoing cases are striking examples of the misleading symptoms, and even lack of symptoms often presented by endometriosis, and the difficulty of making a diagnosis from clinical evidence. Admittedly, such cases are rare, yet they show that unless one is mindful of the possibilities and makes a thorough search of all the organs, an error in treatment or inadequate treatment is not unlikely. This is no less true when the disease process clearly involves the pelvic structures.

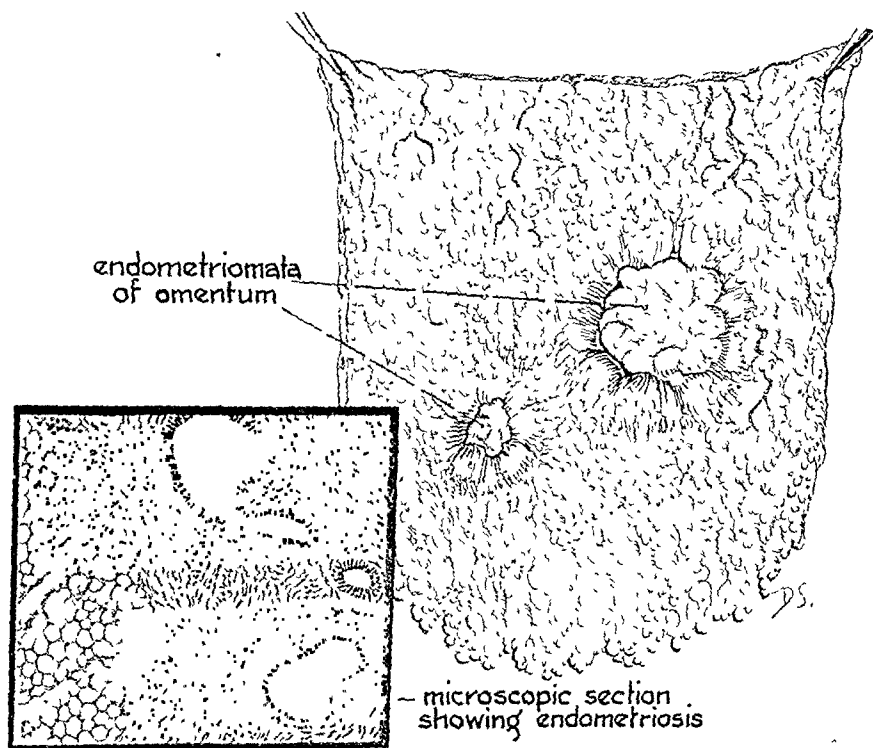


Fig. 3.—Two endometrial tumors of the omentum. No others were found in the abdomen or pelvis. Insert shows microscopic picture of endometrial tissue found in one of the tumors.

One needs merely to review the reported incidence of endometriosis as diagnosed in our hospitals, as compared to the incidence in private clinic practice, to appreciate the fact that it is recognized in only a small proportion of cases. Fallas and Rosenblum<sup>4</sup> report an incidence of 1.62 per cent in pelvic laparotomies in two private hospitals in Los Angeles. This figure is probably low for private hospitals. Perhaps the percentages found in two of the largest private institutions in Memphis are more typical. The records from which they were taken cover only a short period, nevertheless, they are sufficient to illustrate our point.

*The First Metatarsophalangeal Joint.* The metatarsophalangeal joint may present a subluxation if the flexed position of the phalanx is sufficient. If the deformity exists for some time, secondary degenerative changes may occur over the dorsal nonfunctioning portion of the articular surface of the metatarsal.

*Soft Tissue Changes.*—If the deformity becomes fixed the metatarsophalangeal joint presents a true flexion deformity of varying degree with the metatarsal more or less fixed in a dorsal flexed position at the metatarsocuneiform joint or at the first cuneoscaphoid joint or both. Contractures of the capsules of these joints may occur. It is not uncommon to have a true shortening of the flexor hallucis brevis muscle. A callosity often forms at the abnormal point of weight-bearing on the great toe and a callus and bursa may be present over the dorsal prominence of the metatarsal head.

Various primary diseases are associated with this deformity. However, the mechanisms of production of the deformity are, in the main, two in number. The first, and most frequent, is a muscular imbalance acting upon the first metatarsal causing this bone to assume a dorsiflexed position. The plantar flexed attitude of the hallux is secondary. The second mechanism is a muscular imbalance causing a plantar flexed position of the great toe, with secondary upward displacement of the first metatarsal.

#### GENERAL PRODUCTIVE MECHANISMS

##### I. *Primary Dorsiflexion Deformity of the First Metatarsal With Secondary Plantar Flexion Deformity of Hallux, Thirty-Six Examples.*

The upward displacement of the first metatarsal is due to a strong dorsiflexor muscle in the presence of a weak or absent plantar flexor muscle of this bone. Normally, the anterior tibial muscle by virtue of its insertion, raises the first cuneiform and base of the first metatarsal bone and thus can be considered a dorsal flexor of these two bones. The peroneus longus muscle opposes this action by exerting a plantar flexing force upon the base of the first metatarsal. Upward displacement of the first metatarsal can be produced by a strong anterior tibial muscle, or its substitute, in the presence of a weak or absent peroneus longus muscle. With the first metatarsal displaced upward the great toe is actively flexed to establish a point of weight-bearing for the medial portion of the forefoot and to augment the push-off in walking. Weakness of the dorsiflexor muscles of the hallux favor, but are not necessary for, the development of this position of the toe.

##### II. *Primary Plantar Flexion Deformity of the Hallux With Secondary Dorsiflexion Deformity of the First Metatarsal, Six Examples.*

Primary plantar flexion deformity occurs in the foot which is paralyzed except for an Achilles group of variable strength and strong flexors of the toes. The patient utilizes the flexor muscles of the toes

# ELEVATION OF THE FIRST METATARSAL BONE WITH HALLUX EQUINUS

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**A**N INTERESTING deformity of the great toe and first metatarsal bone has been observed for a number of years at the University Hospital. There is no doubt that this condition has been recognized by many observers but specific reference to it is rare in the available literature. Lapidus has recently described this deformity and has presented his conception of the etiologic factors, which are further substantiated by this report, and an operative procedure for its correction.

The purpose of this communication is to offer an explanation of the productive mechanism and to present methods of prevention and correction based upon forty-two examples of this deformity in thirty-eight patients.

## CLINICAL FEATURES

In general, one might describe the deformity as a dorsal flexion deformity of the first metatarsal and a plantar flexion deformity of the great toe. It commonly results from a muscular imbalance of the foot.

In the early stage the deformity is not fixed. Passively the first metatarsal assumes its normal position and the great toe can be dorsiflexed normally. Because the deformity is on the basis of muscular imbalance, the incipient stage is mainly apparent when the patient is weight-bearing and particularly when he is walking. If the inequality of the muscle pull is not marked the deformity may never advance beyond this stage. However, in many cases the causative factors are sufficient to produce a fixed deformity with the subsequent development of pain over the dorsal aspects of the first metatarsal head where a bunion may develop. Even in advanced cases the abnormality is always more marked with active use of the foot in weight-bearing.

*The Great Toe.*—Usually the entire toe is in a position of flexion at the metatarsophalangeal joint. Less commonly the proximal phalanx has a flexed attitude but the distal phalanx is hyperextended. Hallux valgus may be associated.

*The First Metatarsal Bone.*—In the weight-bearing position the head of the first metatarsal is seen to be displaced upward so that the longitudinal axis of the metatarsal shaft may be horizontal or even directed anteriorly and slightly upward. The first cuneiform bone may also be tilted upward. A small exostosis may form on the dorsal surface of the head of the metatarsal.

flexion and thus is a definite contributing factor. The transferred peroneus longus muscle maintained practically normal strength, which is, of course, a prerequisite to the development of the first metatarsal displacement. In exactly similar cases except for weakness of the peroneus longus tendon after transference, the deformity did not develop. The triple arthrodesis is apparently not a factor in the development of the deformity inasmuch as two patients did not have this operation and a third presented the deformity before stabilization was done.

*B. Gastrocnemius and soleus muscles completely paralyzed or very weak. Anterior tibial muscle normal strength, eight examples:*

(a) *Peroneal muscles completely paralyzed, two examples* (Table I, Cases 14 and 15).—Each case presented a calcaneocavovarus deformity. A triple arthrodesis was done in one and a triple arthrodesis plus

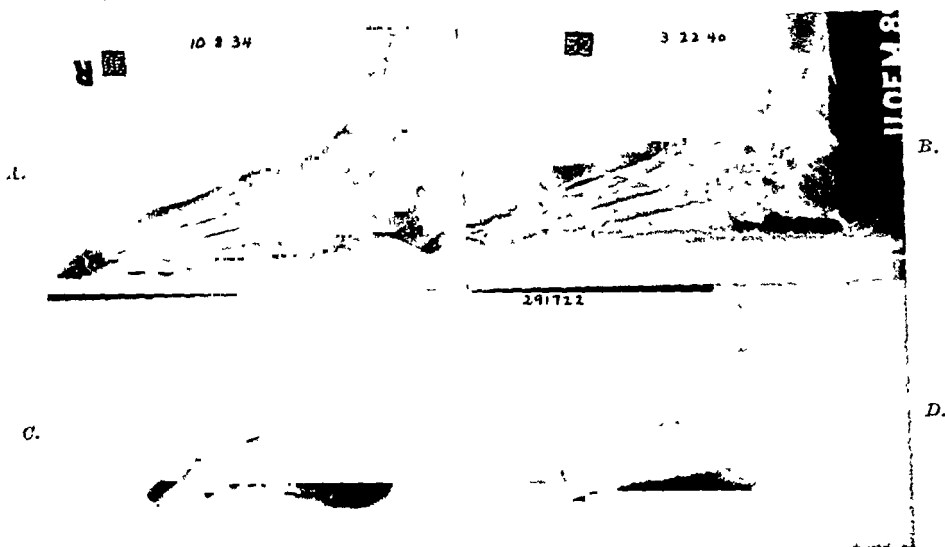


FIG. 1 (Table I, Case 5).—A, Lateral roentgenogram of foot 16 months after a Dunn triple arthrodesis and transference of peroneus longus and brevis into first cuneiform for paralytic pes valgus. The first metatarsal-great toe deformity is minimal.

B, Lateral roentgenogram of foot showing well-developed elevation of first metatarsal with hallux equinus.

C, Photograph of foot showing the deformity; note the skin irritation over the dorsal aspect of the first metatarsal head.

D, Photograph of foot 6 months following operative correction of first metatarsal-great toe deformity.

transference of the tibialis posticus, the flexor hallucis longus, and the flexor digitorum longus tendons to the calcaneus was carried out in the other (Fig. 2).

The cause of the dorsiflexion deformity of the first metatarsal is the strong anterior tibial muscle unopposed by a functioning peroneus longus muscle. The strong flexor hallucis brevis muscle is a secondary factor.

to help steady the foot upon the leg in weight-bearing and to supplement the push-off in walking. The great toe and its flexor muscles assume a large share of this added function and the hallux may be more or less constantly held in plantar flexion with active use of the foot. It is necessary for the head of the metatarsal to displace upward to accommodate for this weight-bearing position of the great toe.

In all cases of plantar flexion deformity of the great toe in type I or II, a strong flexor hallucis brevis muscle was a factor in the production of this deformity.

#### CLASSIFICATION OF CASES ACCORDING TO UNDERLYING DISEASE

##### *Specific Productive Mechanisms*

I. *Anterior Poliomyelitis, Twenty-Seven Examples.*—The primary dorsiflexion deformity of the first metatarsal may be the result of muscular imbalance due to the disease (2 examples) or muscular imbalance created by tendon transference (19 examples). Primary plantar flexion deformity of the hallux occurred only as a result of this disease in our series of cases (6 examples).

A. *Weak or completely paralyzed anterior tibial muscle, strong peroneal muscles; transference of peroneus longus muscle alone or peroneus longus and brevis muscles to the region of insertion of the anterior tibial muscle, thirteen examples* (Table I, Cases 1 to 13 inclusive): Each case had a valgus deformity of the foot. Four patients exhibited a plantar flexion deformity of the first metatarsal bone before operation. The foot was stabilized by triple arthrodesis in all cases except two. The peroneus longus tendon was transferred generally by way of the anterior tibial tendon sheath to a new insertion in the base of the first metatarsal (10 cases), or to the first cuneiform bone (3 cases). If the peroneus brevis tendon was also transferred it was inserted into the base of the second metatarsal (1 case) or into the first or second cuneiform bone (4 cases). From one to six years after the tendon transference, the primary dorsiflexion deformity of the first metatarsal became evident (Fig. 1). The secondary plantar flexion deformity of the hallux appeared concomitantly. The flexor hallucis brevis muscle was very strong in each case except one. Possibly because of this fact, this patient did not develop a plantar flexion deformity of the great toe which maintained a normal relationship with the first metatarsal head, thus not touching the ground in the weight-bearing position (Table I, Case 2).

In this group the primary cause of the deformity is the reversal of action of the peroneus longus muscle upon the first metatarsal brought about by the tendon transference. It is noteworthy that the four patients with plantar flexion deformity of the first metatarsal preoperatively developed a dorsiflexion deformity of this bone after operation. To establish a medial weight-bearing point for the forefoot, the flexor hallucis brevis muscle maintains the great toe in sufficient plantar

E TO ANTERIOR POLIOMYELITIS\*

						OPERATIVE PROCEDURES PRIOR TO ELEVATION OF METATARSAL WITH HALLUX EQUINUS
I.L.	E.H.B.	F.D.L.	F.D.B.	E.D.L.	E.D.B.	
2		1	N	3		Triple arthrodesis; P.L. transfer to base of first metatarsal; P.B. transfer to second cuneiform
2	2	1		2		Triple arthrodesis; P.L. and P.B. transfer to first cuneiform
N	2	0	N	2	3	P.L. transfer to base of first metatarsal; triple arthrodesis; P.B. transfer to second cuneiform
1	2	2		2		P.L. transfer to base of first metatarsal; triple arthrodesis
0		2		0		Vulpius operation; triple arthrodesis; P.L. and P.B. transfer to first cuneiform
3	2	3	N	3	N	Vulpius operation; triple arthrodesis; P.L. transfer to base of first metatarsal
3	N	N	N	N	3	Triple arthrodesis; P.L. transfer to base of first metatarsal; P.B. transfer to second cuneiform
3	N	2	N	4		Vulpius operation; triple arthrodesis; P.L. transfer to base of first metatarsal; P.B. transfer to second metatarsal
N	1	N		N		P.L. transfer to base of first metatarsal
N	N	2		1		Triple arthrodesis; P.L. transfer to base of first metatarsal
3		2		1		P.L. transfer to base of first metatarsal; triple arthrodesis
N						P.L. and E.H.L. transfer to first cuneiform; triple arthrodesis
3		1	1	0	0	Achilles tenotomy; P.L. transfer to base of first metatarsal
N		2	N	0		Triple arthrodesis
2		3		3		Triple arthrodesis; P.T., F.H.L., F.D.L. transfer to calcis
2		N	N	N		Subastragalar arthrodesis; P.L., P.B., and P.T. transfer to os calcis
1		N		2		P.L. and P.B. transfer to os calcis
2		2	2	2		Subastragalar arthrodesis; P.L., P.B., and P.T. transfer to os calcis
1		N				Triple arthrodesis; P.L., P.B., and P.T. transfer to os calcis
N	N	N	1	2	1	P.T., F.H.L., F.D.L., P.L., P.B., transfer to os calcis; triple arthrodesis
4	3	N				F.D.L., P.L., P.B., F.H.L., and P.T. transfer to os calcis; triple arthrodesis
0	0	1	N	4		Achilles tenotomy; Panastragalar arthrodesis
0	0	0		0		Panastragalar arthrodesis
0	0	0	N	0		Panastragalar arthrodesis
0	0	0	N	0		No
0	0	0	1	0		No
0	0	0	0	0		No

A.T.—Anterior tibial  
P.L.—Peroneus longus  
P.B.—Peroneus brevis  
P.T.—Peroneus tertius  
F.H.L.—Flexor hallucis longus  
F.H.B.—Flexor hallucis brevis  
E.H.L.—Extensor hallucis longus  
E.H.B.—Extensor hallucis brevis  
F.D.L.—Flexor digitorum longus  
F.D.B.—Flexor digitorum brevis  
E.D.L.—Extensor digitorum longus  
E.D.B.—Extensor digitorum brevis

TABLE  
EVALUATION OF MUSCLE POWER IN CASES

NO.	PATIENT	FOOT DEFORMITY RESULTING FROM PARALYSIS	G.S.†	P.T.	A.T.	P.L.	P.B.	P.TER.	F.H.L.	F.H.B.
1	R. S.	Planovalgus	1	0	0	1	1		3	1
2	D. D.	Valgus	N	2	0	N	N		N	N
3	L. W.	Valgus	N	0	0	N	N	1	0	N
4	C. B.	Valgus	N	2	0	N	0		1	N
5	A. V.	Equinovalgus	N	0	0	1	1		0	N
6	N. D.	Valgus	1	0	0	N	1		3	N
7	R. H.	Valgus	N	N	0	N	N	N	N	N
8	E. R.	Equinovalgus	N	2	0	N	N		3	N
9	M. H.	Valgus	N	0	0	N	N		N	N
10	W. H.	Calcaneovalgus	3	0	0	N	N		N	N
11	R. S.	Valgus	N	1	0	N	N		3	4
12	E. P.	Valgus	1	1	0	N	2		3	N
13	R. S.	Equinovalgus	1	5	0	N	N		3	1
14	J. V.	Calcaneocavovarus	5	0	N	0	0		0	N
15	M. L.	Calcaneocavovarus	0	2	N	0	0		3	N
16	D. P.	Calcaneocavus	0	1	N	N	N		0	1
17	R. G.	Calcaneocavus	4	N	N	N	N		2	1
18	J. W.	Calcaneocavus	0	1	N	N	N		1	1
19	J. B.	Calcaneocavovarus	3	1	N	1	1		N	
20	J. R.	Calcaneus	5	N	N	N	N		N	N
21	E. P.	Calcaneovalgus	4	1	N	N	N		N	N
22	P. S.	Equinovarus	1	3	5	0	0		0	N
23	W. B.	Equinovarus	N	0	0	0	0		0	N
24	G. D.	Equinovarus	0	0	0	0	0		0	N
25	J. B.		0	0	0	0	0		0	N
26	J. B.		0	0	0	0	0		0	1
27	O. S.	Varus	2	0	0	0	0		0	N

\*Explanation of muscle rating:

N—Normal

1—Very good; a muscle that can overcome gravity and moderate resistance but cannot perform the normal test

2—Good; a muscle that can overcome gravity and slight resistance only

3—Fair; a muscle that can overcome gravity but not resistance

4—Poor; a muscle that can carry out its action only when gravity is eliminated

5—Trace; a muscle that can be felt to contract but cannot move the part

0—Gone; a muscle in which no contraction can be felt.

†Abbreviation for muscles:

G.S.—Gastrocnemius-soleus

P.T.—Posterior tibial



I  
DUE TO ANTERIOR POLIOMYELITIS\*

E.H.L.	E.H.B.	F.D.L.	F.D.B.	E.D.L.	E.D.B.	OPERATIVE PROCEDURES PRIOR TO ELEVATION OF METATARSAL WITH HALLUX EQUINUS
2		1	N	3		Triple arthrodesis; <i>P.L.</i> transfer to base of first metatarsal; <i>P.B.</i> transfer to second cuneiform
2	2	1		2		Triple arthrodesis; <i>P.L.</i> and <i>P.B.</i> transfer to first cuneiform
N	2	0	N	2	3	<i>P.L.</i> transfer to base of first metatarsal; triple arthrodesis; <i>P.B.</i> transfer to second cuneiform
1	2	2		2		<i>P.L.</i> transfer to base of first metatarsal; triple arthrodesis
0		2		0		Vulpus operation; triple arthrodesis; <i>P.L.</i> and <i>P.B.</i> transfer to first cuneiform
3	2	3	N	3	N	Vulpus operation; triple arthrodesis; <i>P.L.</i> transfer to base of first metatarsal
3	N	N	N	N	3	Triple arthrodesis; <i>P.L.</i> transfer to base of first metatarsal; <i>P.B.</i> transfer to second cuneiform
3	N	2	N	4		Vulpus operation; triple arthrodesis; <i>P.L.</i> transfer to base of first metatarsal; <i>P.B.</i> transfer to second metatarsal
N	1	N		N		<i>P.L.</i> transfer to base of first metatarsal
N	N	2		1		Triple arthrodesis; <i>P.L.</i> transfer to base of first metatarsal
3		2		1		<i>P.L.</i> transfer to base of first metatarsal; triple arthrodesis
N						<i>P.L.</i> and E.H.L. transfer to first cuneiform; triple arthrodesis
3		1	1	0	0	Achilles tenotomy; <i>P.L.</i> transfer to base of first metatarsal
N		2	N	0		Triple arthrodesis
2		3		3		Triple arthrodesis; <i>P.T.</i> , <i>F.H.L.</i> , <i>F.D.L.</i> transfer to os calcis
2		N	N	N		Subastragalar arthrodesis; <i>P.L.</i> , <i>P.B.</i> , and <i>P.T.</i> transfer to os calcis
1		N		2		<i>P.L.</i> and <i>P.B.</i> transfer to os calcis
2		2	2	2		Subastragalar arthrodesis; <i>P.L.</i> , <i>P.B.</i> , and <i>P.T.</i> transfer to os calcis
1		N				Triple arthrodesis; <i>P.L.</i> , <i>P.B.</i> , and <i>P.T.</i> transfer to os calcis
N	N	N	1	2	1	<i>P.T.</i> , <i>F.H.L.</i> , <i>F.D.L.</i> , <i>P.L.</i> , <i>P.B.</i> , transfer to os calcis, triple arthrodesis
4	3	N				<i>F.D.L.</i> , <i>P.L.</i> , <i>P.B.</i> , <i>F.H.L.</i> , and <i>P.T.</i> transfer to os calcis; triple arthrodesis
0	0	1	N	4		Achilles tenotomy; Panastragalar arthrodesis
0	0	0		0		Panastragalar arthrodesis
0	0	0	N	0		Panastragalar arthrodesis
0	0	0	N	0		No
0	0	0	1	0		No
0	0	0	0	0		No

A.T.—Anterior tibial  
*P.L.*—Peroneus longus  
*P.B.*—Peroneus brevis  
*P.Ter.*—Peroneus tertius  
*F.H.L.*—Flexor hallucis longus  
*F.H.B.*—Flexor hallucis brevis  
*E.H.L.*—Extensor hallucis longus  
*E.H.B.*—Extensor hallucis brevis  
*F.D.L.*—Flexor digitorum longus  
*F.D.B.*—Flexor digitorum brevis  
*E.D.L.*—Extensor digitorum longus  
*E.D.B.*—Extensor digitorum brevis

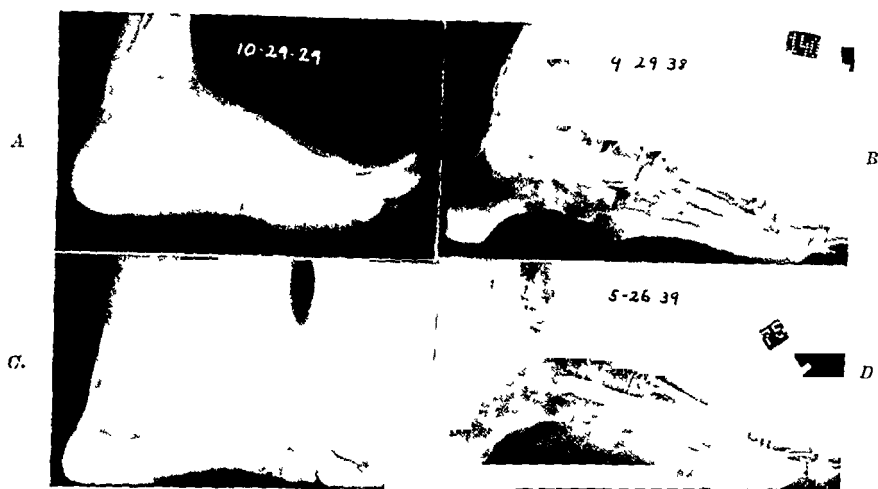


Fig 2 (Table I, Case 15) —A, Lateral roentgenogram of foot 6 months after triple arthrodesis for paralytic pes calcaneocavovarus

B, Lateral roentgenogram of foot showing the elevation of the first metatarsal with hallux equinus

C, Photograph of foot showing the deformity

D, Lateral roentgenogram of foot 6 months after operative correction of first metatarsal-great toe deformity (In this case the tibial graft was placed medially)

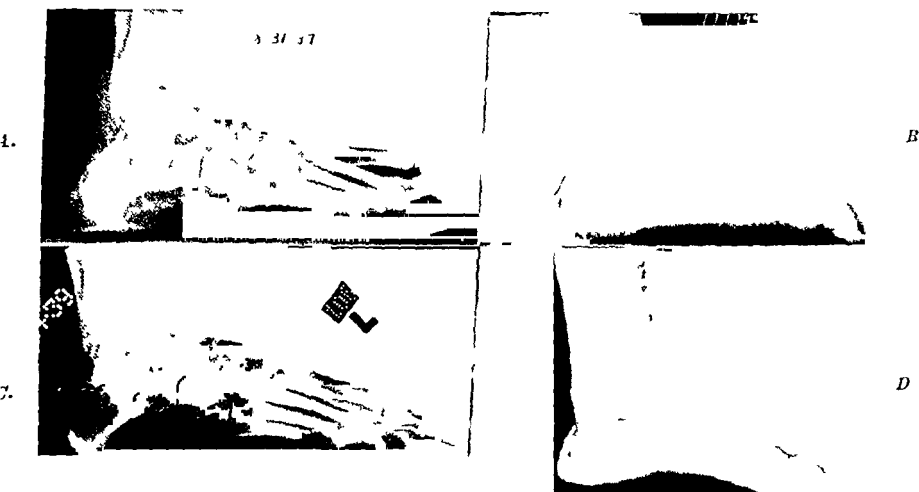


Fig 3 (Table I, Case 16) —A, Lateral roentgenogram of foot 10 years after astragalocalcaneal arthrodesis and transference of peroneus longus, peroneus brevis, and posterior tibial tendons to calcaneus for paralytic pes calcaneocavus, the elevated first metatarsal with hallux equinus is well developed

B, Photograph of foot as shown in A

C, Lateral roentgenogram of foot 6 months after operative correction of first metatarsal-great toe deformity

D, Photograph of foot 15 months after operative correction of first metatarsal deformity.

(b) *Peroneal muscles normal strength. Transference of peroneal tendons to os calcis, six examples* (Table I, Cases 16 to 21 inclusive).—Four cases had calcaneocavus deformities of the foot and one patient presented a pes calcaneocavovarus. A triple arthrodesis was done. Both peroneal tendons with or without other tendons were transferred to the os calcis in each case. The dorsal flexed position of the first metatarsal bone developed from two to twelve years after the tendon transference (Fig. 3).

Due to the transference of the peroneus longus the strong anterior tibial muscle causes dorsiflexion of the first metatarsal. The development of this deformity before the triple arthrodesis in 2 patients of this group again demonstrates that the stabilization is not a necessary factor. A strong flexor hallucis brevis muscle is contributive.

C. *Strong flexor hallucis brevis muscle. Gastrocnemius-soleus muscles strong, moderately weak, or paralyzed. Otherwise lower extremity essentially flail, six examples* (Table I, Cases 22 to 27 inclusive): The extremities were supported by braces. The flexor digitorum brevis muscle was also generally active. The gastrocnemius-soleus muscle group was completely paralyzed in three of the extremities while it was moderately weak in one and had normal strength in two. One patient had a strong flexor hallucis longus. To correct deformity and to stabilize the foot a panastragalar arthrodesis was done in three patients. To correct the metatarsal displacement the flexor hallucis longus in the one patient was sectioned without result (Fig. 4).

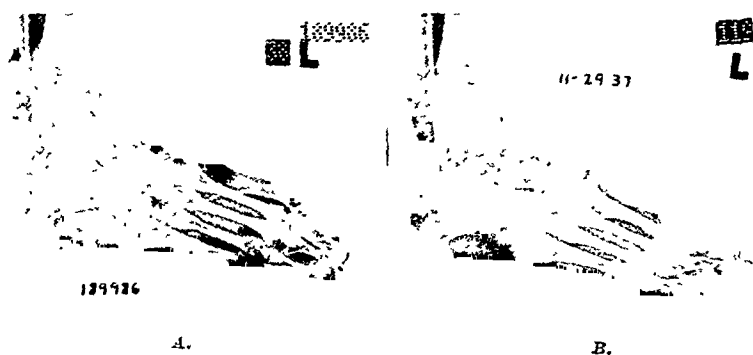


Fig. 4 (Table I, Case 27).—A, Lateral roentgenogram of foot 3 years after panastragalar arthrodesis for paralytic pes equinovarus, the first metatarsal-great toe deformity is well developed.

B, Lateral roentgenogram of foot 2 months after operative correction of first metatarsal-great toe deformity. (The tibial graft was placed medially in this case.)

The strong flexor hallucis brevis muscle is the primary cause of the deformity, producing a plantar flexion deformity of the great toe. This muscle supplements the Achilles group of muscles in walking or when the action of the latter is absent, acts as a plantar flexor to gain some power of push-off in walking. In the standing position the muscle is

again very active as an aid in balance. The first metatarsal bone, of necessity, dorsiflexes when the hallux assumes this position.

II. *Congenital Talipes Equinovarus, Seven Examples.*—A primary dorsal flexion deformity of the first metatarsal bone and secondary plantar flexion deformity of the great toe may develop.

A. *Deformity well corrected. Persistent imbalance of peroneal muscles and tibial muscles, one example:* This patient was first seen because of a mild recurrence of equinovarus deformity. Tibial muscles possessed normal strength but the peroneal muscles were very weak. A triple arthrodesis was done and resulted in good correction. Six months later, on standing and walking only, the first metatarsal bone was dorsiflexed and the hallux plantar flexed. With the foot at rest there was no evidence of this deformity.

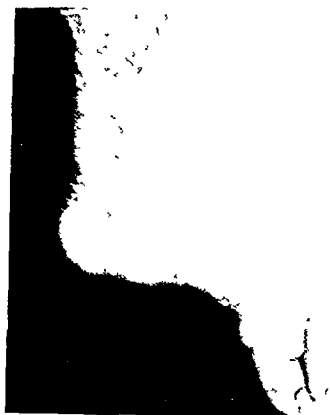


Fig. 1 C.—Photograph showing the deformity as in Fig. 4 A.

B. *Residual severe deformity consisting of equinus of the hind foot and dorsiflexion of the forefoot (Rocker feet), six examples:* The patients varied in age from 6 months to 5 years when treatment was started. All presented severe talipes equinovarus which either responded to conservative treatment and then recurred or failed to respond from the start to this form of therapy. In two cases there were long periods when the patients were not seen. Corrective soft tissue operations followed by either the Hoke or Dunn type of triple arthrodesis were done in all cases. In performing the stabilization in one patient both peroneal tendons were sectioned for purposes of exposure and were sutured at the completion of the operation. The metatarsal deformity gradually developed before the stabilization in four feet and after the stabilization in two (Fig. 5).

The metatarsal and great toe deformity in this group is, again, due to the imbalance which exists between the peroneus longus and the anterior tibial muscles. In the uncorrected congenital talipes equino-

varus the peroneal muscles are weak and the tibial muscles are strong. After complete correction of the deformity this muscle imbalance may persist and account for a dorsiflexed first metatarsal bone and a plantar-flexed great toe which may, at first, be present only upon use of the foot.

Faulty manipulative corrections of a congenital talipes equinovarus may, unfortunately, produce the so-called rocker foot by forcibly stretching the ligaments and capsules which support the plantar aspects of the mid-tarsal joints. The hind foot remains in equinus and inversion while the forefoot is dorsiflexed and sometimes abducted. The action of the peroneus longus muscle is further weakened by the mechanical



Fig. 5.—A, Lateral roentgenogram of foot 3 months after a Dunn triple arthrodesis for congenital talipes equinovarus.

B, Lateral roentgenogram of foot 6 years later, showing a markedly elevated first metatarsal with hallux equinus.

C, Photograph of foot showing the first metatarsal-great toe deformity with a marked dorsal bunion over the first metatarsal head.

D, Lateral roentgenogram of foot 5 years after operative correction of first metatarsal-great toe deformity.

interference imposed by such a deformity. The anterior tibial muscle, strong from the beginning, becomes more powerful with attempts of the patient to gain dorsiflexion of the entire foot. Thus, the first metatarsal bone is gradually pulled into more relative dorsiflexion than the rest of the forefoot. The great toe is plantarflexed by its two flexor muscles to provide a point of weight-bearing medially and to aid the push-off which is limited and weakened by the equinus of the heel.

III. *Osteomyelitis of Os Calcis, Three Examples.*—The osteomyelitis was due to pyogenic organisms in two cases and tuberculosis in one. The disease was quiescent in each case and the patients had been walking upon the foot for years. Either because of operative removal or

again very active as an aid in balance. The first metatarsal bone, of necessity, dorsiflexes when the hallux assumes this position.

II. *Congenital Talipes Equinovarus, Seven Examples.*—A primary dorsal flexion deformity of the first metatarsal bone and secondary plantar flexion deformity of the great toe may develop.

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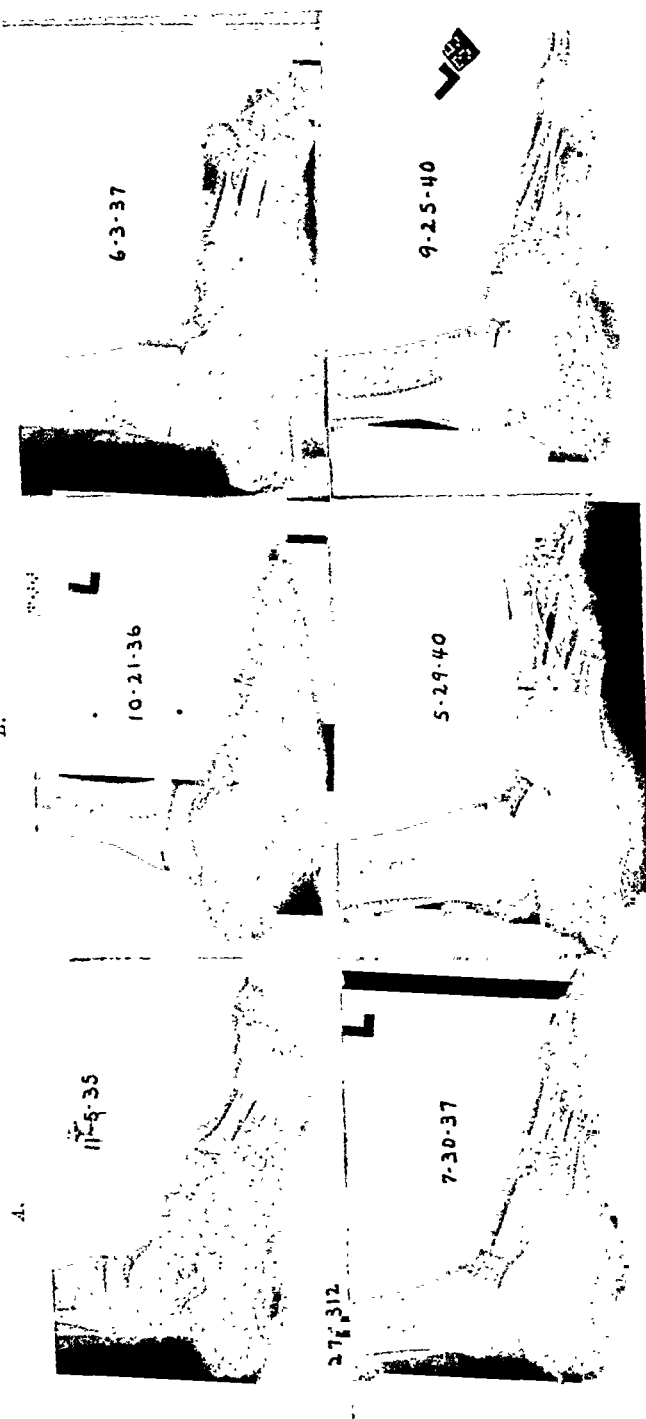


Fig. 4 C.—Photograph showing the deformity as in Fig. 4 A.

B. *Residual severe deformity consisting of equinus of the hind foot and dorsiflexion of the forefoot (Rocker feet), six examples:* The patients varied in age from 6 months to 5 years when treatment was started. All presented severe talipes equinovarus which either responded to conservative treatment and then recurred or failed to respond from the start to this form of therapy. In two cases there were long periods when the patients were not seen. Corrective soft tissue operations followed by either the Hoke or Dunn type of triple arthrodesis were done in all cases. In performing the stabilization in one patient both peroneal tendons were sectioned for purposes of exposure and were sutured at the completion of the operation. The metatarsal deformity gradually developed before the stabilization in four feet and after the stabilization in two (Fig. 5).

The metatarsal and great toe deformity in this group is, again, due to the imbalance which exists between the peroneus longus and the anterior tibial muscles. In the uncorrected congenital talipes equino-

B.



D.

E.

F.

Fig. 7 (Case 1).—A, Lateral roentgenogram of foot 5 months after plantar stripping and transference of posterior tibial tendon to dorsum for pes cavus of moderate degree.  
 B, Lateral roentgenogram of foot 11 months later showing marked rocker foot deformity; a triple arthrodesis has been done but the marked pes planovalgus returned promptly.  
 C, Lateral roentgenogram of foot showing marked elevation of first metatarsal with hallux equinus; the mid-tarsal joint did not fuse, tibial graft has displaced out of its prepared bed.  
 D, Lateral roentgenogram of foot showing recurrence of the first metatarsal-great toe deformity because of the displaced tibial graft.  
 E, Lateral roentgenogram of foot 4 months after mid-tarsal osteotomy with bone grafts dorsally, correcting first metatarsal-great toe deformity.  
 F, Lateral roentgenogram of foot 5 months after plantar stripping and transference of posterior tibial tendon to dorsum for pes cavus of moderate degree.

destruction or both there was considerable loss of substance and deformity of the calcaneus. Because of infection and operations all presented considerable scarring about the hind foot. The infection had involved the ankle joints in the three cases causing a bony ankylosis. The subastragalar joint was ankylosed by bone in one and by fibrous tissue in two cases. The anterior tibial muscle possessed normal strength. The peroneal muscles were caught in scar tissue in one case, were of questionable strength in one, and had good power in the third. The flexor hallucis longus muscle was moderately weak in two cases and had no apparent action in one. The flexor hallucis brevis muscle possessed normal power in all cases. The dorsal flexion of the first metatarsal bone and plantar flexion of the hallux gradually developed. This deformity varied in degree and was always most marked on weight-bearing and walking (Fig. 6).



Fig. 6.—A, Lateral roentgenogram of foot showing the ankylosed ankle and the marked deformity of the os calcis due to chronic, inactive, pyogenic osteomyelitis; the elevated first metatarsal with hallux equinus is well advanced.

B, Lateral roentgenogram of foot 1 year after operative correction of first metatarsal-great toe deformity.

The possible causes of the deformity in these cases seem to be three in number. Due to the considerable scarring about the heel the peroneus longus muscle may have been somewhat adherent to the scar tissue as it definitely was in one patient. The peroneal muscles may be further weakened by working at a mechanical disadvantage due to the deformity of the hind foot. The third factor is the ankylosis of the ankle with consequent loss of push-off from the Achilles group. This leads to the development of the flexors of the great toe, particularly the flexor hallucis brevis muscle, as secondary propelling muscles. All of these factors may be operative in these cases to explain the great toe-first metatarsal deformity upon the basis of muscular imbalance.

*IV. Cavus Feet, Three Examples.*—Two patients with cavus feet developed a primary dorsiflexion deformity of the first metatarsal bone with secondary plantar flexion deformity of the great toe. The etiology of the pes cavus was obscure, although the second patient had a spina bifida occulta.

*CASE 1.*—The first patient had bilateral pes cavus of moderate degree associated with mild weakness of the peroneal muscles. The plantar fascia was contracted and



The metatarsal deformity apparently is primary and may be produced by essentially the same mechanism as in a rocker foot. The overactivity of the anterior tibial muscle to produce dorsiflexion and inversion in a pronated valgus foot overbalances the action of the peroneus longus upon the first metatarsal.

VI. *Paralytic Pes Planovalgus Associated With Recklinghausen's Neurofibromatosis, One Example.*—This patient presented a rather severe pes planovalgus which apparently resulted from involvement of the spinal cord by the neurofibromatosis. Definite paresis of the posterior tibial and gastrocnemius muscles was demonstrable. Conservative treatment failed and a triple arthrodesis was performed. The *peroneal tendons were sectioned in performing this procedure* because the operator reasoned that they were deforming factors. This was an error in judgment as subsequent events proved. The weakness of the plantar flexors of the foot was increased with a definite calcaneal type of foot developing. Eight months after operation a well-marked dorsal flexion deformity of the first metatarsal and plantar flexion attitude of the great toe was present.

The metatarsal deformity is primary and is due to the action of a strong anterior tibial muscle unopposed by a peroneus longus muscle. The flexor muscles of the great toe were utilized to enhance the pushoff mechanism in walking and also were used to plantarflex the great toe for a medial weight-bearing point. This case is comparable to the cases in Group B (a) caused by anterior poliomyelitis.

#### TREATMENT

*Prophylaxis.*—Nineteen cases of this deformity occurred as a result of tendon transference in anterior poliomyelitis. In these instances the balanced and opposing actions of the peroneus longus and anterior tibial muscles upon the first metatarsal had been underestimated before proceeding with tendon transference. Before transference of the peroneus longus tendon the effect of the loss of its normal action upon the first metatarsal should be carefully considered.

With paralysis of the anterior tibial muscle in a case adapted to tendon transference, the peroneus longus tendon or both peroneal tendons should be transferred to the region of the third metatarsal base or third cuneiform bone rather than to the region of insertion of the anterior tibial tendon. By this procedure the objectives of the tendon transference will be gained without resultant deformity of the first metatarsal bone. Another method that may be suggested is the transference of the peroneus brevis tendon to the anterior tibial tendon insertion, leaving the peroneus longus undisturbed. A triple arthrodesis is, of course, always indicated (Group I, A).

In cases of weak or paralyzed Achilles group of muscles with strong anterior tibial and peroneus longus muscles, the latter muscle should

overaction of the posterior tibial muscles was thought to be a contributing factor. Bilateral stripping of the plantar fascia and intrinsic muscles from the os calcis and transference of the posterior tibial tendons to the base of the third metatarsal bones were done. Within four months bilateral marked rocker foot resulted in a complete reversal of the original deformity. A triple arthrodesis of each foot failed to stabilize the foot in good position and the rocker feet continued. One year after the latter procedure, dorsal flexion deformities of both first metatarsals associated with plantar flexion deformities of the great toes were noted. Bunions were present over the dorsal aspects of the metatarsal heads (Fig. 7).

The reversal of the deformity from pes cavus to pes planovalgus in this case was due to the posterior tibial tendon transference to the dorsum of the foot. The dorsiflexed position of both first metatarsals with plantar flexion of the great toes was caused by the same muscular imbalance as in rocker feet complicating congenital talipes equinovarus.

CASE 2.—The second patient presented bilateral pes cavovarus associated with claw toes. The deformity was more marked in the left foot and the subsequent discussion refers to this foot. Pain over the plantar surface of the first metatarsal head was present and on weight-bearing he protected this joint by inverting the foot. No definite muscle weakness in the foot was apparent. The deformity was largely confined to the forefoot, the hind foot being essentially normal in appearance. The following operation was done upon the foot: arthrodesis of the first metatarsocuneiform joint with removal of wedges of bone from this joint to correct the downward displacement of the first metatarsal; transference of the tendon of the extensor hallucis longus to the neck of the first metatarsal; arthrodesis of the interphalangeal joint of the great toe; and dorsal capsulotomy of the first metatarsophalangeal joint to allow correction of the clawing of the great toe. Eighteen months later there was a dorsiflexion deformity of the first metatarsal with plantar flexion of the great toe. The patient continued to complain of pain in the first metatarsophalangeal joint.

The cause of the great toe-metatarsal deformity is not exactly clear. Although the tendon transference resulted in marked weakness of dorsiflexion of the great toe, the flexors of this toe also became weak. A very plausible explanation, but one which is not definitely proved by postoperative roentgenograms, is the possible interruption of or slowing of growth from the dorsal portion of the epiphyseal line of the first metatarsal bone caused by the wedge osteotomy of the metatarsocuneiform joint. The base of the wedge of bone removed from this joint was, of course, dorsal and trauma to the dorsal portion of the metatarsal epiphysis might have resulted. The persistent pain over the plantar surface of the first metatarsal head might also explain the deformity inasmuch as protection of this painful area would require overuse of the tibialis anticus muscle in order to lift the first metatarsal head from the weight-bearing surface.

V. *Pes Planovalgus, One Example.*—Following a twisting injury to the foot and ankle the patient developed a painful pronation of the right foot. There was considerable spasm of the peroneal muscles and of the long extensor muscles of the toes. Marked limitation of inversion and eversion of the foot was noted. The foot did not respond to conservative management and a triple arthrodesis was done. The deformity gradually recurred and a dorsal flexion deformity of the first metatarsal and plantar flexed great toe appeared. The stabilization had relieved the peroneal spasm. The tibialis anticus muscle was overactive during active use of the foot.

sule and the cartilage is removed. With a thin osteotome a rectangular section of bone  $\frac{1}{4}$  to  $\frac{3}{8}$  inch deep is removed from the dorsal aspects of the contiguous bones. These two sections of bone are cut into small pieces. The first metatarsal bone is manipulated into its normal position where it is held by an assistant. This replacement results in a wedge-shaped defect in the joint as the dorsal aspects of the contiguous bones swing apart. A bone graft of sufficient size to fill the rectangular defect and to bridge the dorsal gap in the joint is removed from the tibia and pounded into the prepared bed, maintaining the correct position of the metatarsal. Any space remaining in the joint is filled with small bone grafts. If arthrodesis of both the first metatarsocuneiform and first cuneoscaphoid joints seems advisable the technique is the

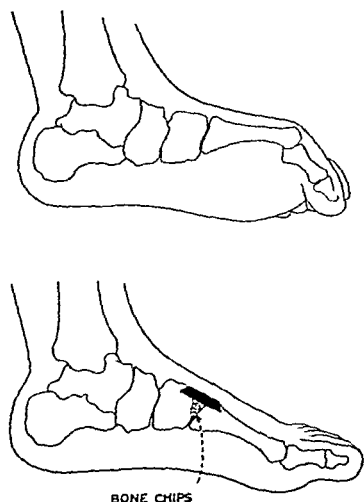


Fig. 8.—Drawings to illustrate the arthrodesis of the first metatarsocuneiform joint, utilizing a tibial bone graft and bone chips, to correct elevation of the first metatarsal with hallux equinus, the deforming muscle should be transferred to the mid-foot if the first metatarsal displacement is primary.

same, the tibial bone graft extending from the scaphoid bone across the first cuneiform into the base of the first metatarsal. If there is a fixed plantar flexion deformity of the great toe it usually responds to manipulation. In a small minority of cases a capsulotomy of the plantar aspect of the first metatarsophalangeal joint was also necessary. The foot is immobilized in a plaster cast with the corrected position of the first metatarsal well supported. Ankylosis is usually present in eight weeks (Fig. 8).

Other operative procedures have been used in correcting this deformity inasmuch as the treatment must be individualized for each case. Thus the correction of the first metatarsal deformity may be done at the mid-tarsal area as part of an osteotomy or triple arthrodesis which is necessary to correct other deformities and to stabilize the foot (Table II, Miscellaneous operations).

not be transferred to the os calcis unless the anterior tibial tendon is transferred to the mid-foot (Group I, B,b).

*Treatment of the Deformity.*—If the muscle imbalance is not marked, the deformity may never become severe enough to warrant operative correction. In cases showing progressive deformity of the great toe and first metatarsal, operative correction is simplest when done early before the deformity has become fixed. Transference of the deforming muscle, either the anterior tibial or transferred peroneus longus, to the third metatarsal base may correct the dorsal flexion of the first metatarsal.

If the first metatarsal deformity has existed for some time, it becomes more or less fixed and more radical surgery is often indicated. The deforming tendon should be transferred to the mid-foot as already referred to and an arthrodesis of the joint or joints at which the dorsiflexion occurs should be performed, correcting the metatarsal displacement. This requires, as a rule, a corrective arthrodesis of the first metatarsocuneiform joint or the first cuneoseaphoid joint or both. This operation has given very satisfactory results in our experience (Table II). The dorsal aspect of the joint is opened by reflexion of the cap-

TABLE II  
RESULTS OF OPERATIVE CORRECTION OF DEFORMITY

OPERATION	AVERAGE TIME POST- OPER- ATIVELY (IN MONTHS)	GOOD		FAIR		POOR		TOTAL NUMBER OF EACH OPERA- TION
		NO.	%	NO.	%	NO.	%	
Transference of de- forming tendon	15	3	50	2	33	1	17	6
Corrective arthrodesis utilizing tibial graft dorsally	21	11	73	3	20	1	7	15
Transference of de- forming tendon plus corrective arthrode- sis utilizing tibial graft dorsally	3	1	100					1
Miscellaneous opera- tions*	19	5	71	1	14	1	14	7
Summary		20	69	6	21	3	10	29

\*Miscellaneous operations

- |  |         |
|--|---------|
| 1. Transverse osteotomy of proximal metatarsal shaft with dorsal tibial graft  | RESULTS |
| 2. Transverse mid-tarsal osteotomy with rotation of forefoot to correct first metatarsal displacement and removal of wedge of bone to correct adduction; transference of deforming tendon (transferred peroneus longus tendon) | Fair    |
| 3. Corrective panastragalar arthrodesis to correct talipes calcaneovalgus, section of deforming tendon (anterior tibial tendon)  | Good    |
| 4. First cuneiform scaphoid fusion with reversal of plantar wedges of bone (talonavicular fusion); capsulotomy of first metatarsophalangeal joint to correct flexion deformity of hallux                                       | Good    |
| 5. Triple arthrodesis, manipulation of forefoot into plantar flexion; tibial graft to defect in dorsal aspect of talonavicular joint   | Good    |
| 6. First metatarsocuneiform arthrodesis, section flexor muscles of great toe; capsulotomy of first metatarsophalangeal joint to correct flexion deformity of hallux  | Good    |
| 7. Transverse mid-tarsal osteotomy; manipulation of forefoot into plantar flexion; tibial graft to defect in dorsal aspect osteotomy line  | Poor    |

# A CASE OF LIVEDO RETICULARIS AND VASOSPASM TREATED BY SYMPATHECTOMY, WITH SOME NOTES ON SYMPATHETIC ANESTHESIA IN LABOR

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**L**IVEDO reticularis is a rather uncommon circulatory disorder of the skin which has been recognized for many years but the mechanism of which is poorly understood. It is characterized by a reticular bluish mottling of the skin which is intensified by cold and by dependency of the affected part. Closely allied to this condition is the so-called livedo racemosa in which there are raised or palpable cutaneous lesions in a distribution corresponding to the bluish areas in livedo reticularis. Also closely related is erythema ab igne, a condition in which a more or less permanent reddish or brownish discoloration of the same general pattern occurs as a result of exposure to heat.

The classification of livedo reticularis which Williams and Goodman<sup>1</sup> suggested is a very helpful one. These authors divided the cases into three groups. *Cutis marmorata*, the commonest form, occurs as a general rule rather diffusely over the body, is increased by cold and disappears when the body is warm, and is most frequent in infants, often disappearing as the child grows older. *Livedo reticularis idiopathica* is a more intense mottling which generally persists with variation in degree regardless of ordinary changes in the temperature of the skin. *Livedo reticularis symptomatica* is a similarly persistent mottling associated with some other disease which may affect the superficial vascular bed, such as the erythema induratum type of tuberculid,<sup>2</sup> syphilis,<sup>3</sup> or periarteritis nodosa.<sup>4</sup>

The case which I am reporting represents an unusual type of vasospastic disease in which livedo reticularis was present in the lower limbs. Because of the absence of pain with the uterine contractions of labor in this patient after she had undergone bilateral lumbar sympathectomy, I have been stimulated to investigate local anesthesia of the sympathetic nerves for the relief of pain in labor.

## CASE REPORT

H. S., an 18-year-old white girl, came to the Johns Hopkins Hospital on May 29, 1940, complaining of bluish mottling of both lower extremities and of coldness and numbness of both feet. Her general health had been good. Two years previously, during the winter, a friend had called her attention to a bluish discoloration about both ankles. When first noticed it was evenly distributed in both legs and gradually spread in a symmetrical fashion down into the feet and farther up the legs.

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## SUMMARY

Forty-two examples of elevation of the first metatarsal with hallux equinus have been reviewed. The modes of production and methods of prevention and operative correction of the deformity are presented.

The deformity is caused by a muscular imbalance of the foot which is the result of various primary diseases. An imbalance of muscles acting upon the first metatarsal caused the deformity in 86 per cent of the cases while 14 per cent were the results of muscular imbalance of the great toe.

The primary disease was anterior poliomyelitis in 64 per cent of the examples. Tendon transference accounted for the deformity in 70 per cent of the cases in this group (45 per cent of the total series). Before transference of the peroneus longus tendon careful consideration should be directed to the effect of such transference upon the first metatarsal. This tendon should not be transferred to the region of insertion of the anterior tibial tendon nor should it be transferred to the os calcis without regard for a strong anterior tibial muscle.

The results of operative correction of this deformity have been relatively good.

The author wishes to express his appreciation to Dr. C. E. Badgley, Dr. Martin Batts, and Dr. R. E. McCotter for their help and advice in the preparation of this manuscript.

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On July 25, the second, third, and fourth lumbar sympathetic ganglia on the right side, with the intervening chain, were excised through the usual extraperitoneal approach. After this operation no mottling was noted in the right lower extremity and it remained warm and dry, whereas mottling persisted in the left, and the left foot was usually cool and wet though covered by bedclothes. When the legs hung down, however, a faint pink mottling appeared in the right leg and foot. Even in a hot room (30.4° C.) the difference in temperature of the two lower extremities was striking: the toes were 6.5° warmer on the right side, the ankle 3° and the patellar region 2° C. The same operation was carried out on the left side on August 1, and she was discharged on August 7.

Her feet have remained warm and dry, there has been no discomfort or numbness, and she has had no discoloration except a faint pink mottling when her legs are dependent. She has gone through two winters without any difficulty. When her legs are dependent a faint mottling is present which is less extensive than it was before operation, the reticulations are much finer, and the color is an inconspicuous bright pink. The mottling disappears slowly when she lies down, a little more rapidly when her limbs are elevated; it gradually appears when the limbs are hanging down, a little more slowly when a venous tourniquet is placed about the thigh when the patient is recumbent.



FIG 1.—Photograph of a water color of the patient's right lower extremity.

The patient had her first child in August, 1941. When a show appeared she consulted her physician and was surprised to be told that she was having strong uterine contractions and was in active labor. She was admitted to a hospital, labor progressed rapidly, and she was delivered spontaneously of a normal infant. She said that she had no pain at all with uterine contractions up to the time of expulsion of the baby.

#### DISCUSSION

Kaposi,<sup>1</sup> who apparently first used the term livedo to designate localized and limited areas of cyanotic mottling in contradistinction to generalized cyanosis, felt that the mottling was due to distension of the veins. The superficial venous network does not, however, correspond to the pattern of livedo reticularis. Renaut<sup>2</sup> made studies of the arrangement of blood vessels in the skin by injections of Prussian blue, during which there first appeared rounded blue patches which he felt outlined the bases of vascular cones, each of which was fed by a deep artery at its apex and which represented areas of maximal circulation. As the injection was first being made these rounded areas were separated by

Recently it had been present in the lower half of both thighs. When she arose in the morning the mottling was slight and became more noticeable after she had been on her feet for a short while. She thought it was increased by exposure to cold, it was less prominent during the warm summer months but became even more extensive when cold weather returned. She said that the discoloration became less apparent when she warmed her legs before a fire or under bedclothes. During the winter in which the mottling was first observed she had also begun to complain of coldness of her feet and legs; she could not recall which came first. On slight exposure to cold the feet and legs would become extremely cold, and often there would be a mild aching tired feeling in the legs and feet and an annoying numbness of the feet and ankles. Emotional excitement did not seem to cause her feet to become cold. She thought that her feet and hands perspired more than normally. She had no edema or ulceration. Her hands were generally warm and became cold only on prolonged exposure to extreme cold. In recent months she had noted a very faint mottling on the dorsum of her left hand. It was of interest that the patient, as well as other members of her family, was accustomed to sitting with her feet on the rail of a stove when she came indoors on a cold day. No other members of the family had similar complaints. The family did not recall any mottling during her infancy.

When she was first seen in the outpatient department on a cool day but after she had been in a warm room for an hour or more, her lower extremities presented a striking appearance. There was a dirty blue reticular mottling beginning in the mid thighs and covering the entire legs and feet. The central areas within the cyanotic rings were extremely pale and the appearance was much like that often seen in cadavers. The entire discolored area was very cold, the upper halves of the thighs were warm. The femoral arteries pulsated well. At times it was thought that a weak pulsation in the left posterior tibial artery could be distinguished, but this was not certain. No right posterior tibial and neither dorsal pedal pulsation could be felt. On elevation of the legs the pale areas increased in pallor and the mottled blue gradually became less prominent and eventually disappeared. The mottling was intensified when the limbs hung down. The hands were moderately warm and the radial pulses full, and there was no mottling of the upper extremities or trunk.

Two days later skin temperature studies were carried out. After the patient had been lying down in a warm room for some time the feet were slightly cool, the legs warm. The dorsal pedal pulsations were small but easily felt, the posterior tibial pulsations were full. There was a pinkish blue mottling up to the knees. On exposure to cold (room temperature  $20^{\circ}\text{C}$ ) the toes cooled to about room temperature, the temperature in the fingers dropped to  $28^{\circ}\text{C}$ , the mottling became more intense and extended up into the thighs, and the pinkish blue color gave way to a dusky blue. A very faint mottling appeared on the dorsum of the left hand. The dorsal pedal pulsations became almost imperceptible. When the body was warmed with blankets and heating pads, the exposed lower extremities gradually became warm, the pulses became stronger, and the mottling disappeared. After an hour and a quarter of body heating the temperature of the toes rose to  $34^{\circ}\text{C}$ .

She was admitted to the hospital on July 23, 1949, the mottling had been less prominent during the previous summer, but it was now very noticeable even during hot weather. Although it was a very hot day the feet were cool and the mottling was present. Fig 1 is a photograph of a water color made on a hot day after brief exposure in a cold room. When vasospasm was more complete the mottling was even more extensive than is here represented. When there was moderate vasospasm a brilliant red reaction could be obtained over both the pale and the livid areas by pricking into the skin a solution of 1:1,000 histamine. No reaction occurred when 1 per cent mecholyl was pricked into the skin. These tests were not repeated when vasospasm was extreme.

The impression was that the patient had severe vasospasm and livedo reticularis of both lower extremities.



mottling after body warming or sympathectomy, as in my case (although the discoloration is now pink and not blue) is due to the fact that in some instances the atony and dilatation of the capillaries may be more or less permanent. In order to explain the disappearance of the livedo on elevation of the affected limb it seems best to assume that the venules draining the capillary bed in the peripheral annular zones where there is reduced blood flow and capillary atony are likewise somewhat dilated. When the limb is dependent the increased venous pressure would exaggerate this dilatation and stagnation in the venules and would increase the livedo; when the limbs are elevated these venules would empty and diminish the mottling. This explanation would account for the changes in appearance with dependency and elevation of the limb after sympathectomy has been performed and any normal vasoconstrictor effects of dependency presumably have been eliminated.

It is interesting that Cavafy<sup>15</sup> in 1883 wrote: "I think the condition is probably due to a vasomotor neurosis, allied to the local asphyxia of Raynaud, but the share taken in its production by arteries and veins is not easy to apportion. In temporary mottling from cold we have probably to do with spasm of the terminal arterioles of the skin and consequent overfilling (from diminution of pressure *a tergo*) of capillaries and veins. . . ."

Barker, Hines, and Craig<sup>10</sup> have recently reported thirteen cases of livedo reticularis and have expressed the opinion that there are usually organic changes in the arterioles of the skin as well as chronic vasospasm. Several of their patients had ulcers of the legs and superficial gangrene of the toes. They performed lumbar sympathectomy in three cases. In two, in which there was gangrene of the toes, the feet became warm, the toes healed, no further gangrene developed, and the livedo almost completely disappeared. In the third, in which there was an ulcer of the leg and gangrene of several toes, the operation was followed by healing of the ulcer and toes but the ulcer reappeared after a year and amputation was eventually necessary. In this case the livedo persisted but the color of the livid areas was pink except on exposure to extreme cold.

The fact that my patient went through the first stage of labor without feeling any pain with uterine contractions was a very stimulating and somewhat surprising occurrence. The course of the afferent pain fibers from the uterus is not fully understood. Whether they pass from the superior hypogastric plexus directly into the lumbar sympathetic chains or whether all or part of them pass up through the aortic plexus to enter the sympathetic chains at a higher level, is not known. With regard to my patient one cannot be certain whether there was a causal relationship between the excision of the lumbar sympathetic chains and the absence of pain with uterine contractions. She certainly reacted normally to other painful stimuli.

I know of one other instance in which a patient on whom bilateral lumbar sympathectomy had been performed has recently gone through

pale tracts which he thought were the peripheral portions of the vascular cones and represented areas of reduced circulation. As the injection proceeded, these areas also became blue. He thought that venous stasis might produce a dusky reticular network corresponding to the areas of reduced circulation. This explanation of the anatomic background of livedo was accepted by Adamson<sup>7</sup> and others. Lewis<sup>8</sup> was unable to repeat these observations with dye injections of the skin, nor was he able to substantiate them with observations of natural injections of the skin following release of pressure after an arm had been emptied of blood with an Esmarch bandage. Yet he concluded that the evidence pointed to a "correspondence between areas of mottling and main arteriolar territories, the maximal points of supply being in the center of the paler areas. This excess of blood flow, slight as it may be, would explain an associated increase of minute vessel tone and pallor. Given that the marginal areas are areas to which blood flow is slightly less, then they would be more susceptible to damage, and here the tone of the vessels, originally low, would tend to become more or less permanently inefficient, leading to quite distinct changes in responsiveness, changes that might even become associated with refractoriness." Although Lewis was unable ordinarily to detect anything but negligible and inconstant differences in temperature between the pale and the colored areas, as might be expected if the difference in flow is slight, he did find that the pale areas in a case of erythema ab igne were, on an average,  $0.08^{\circ}$  C. warmer than the dark areas, indicating, if anything, a slightly greater blood flow in the pale areas.<sup>8, 9</sup> Lewis stated that capillaries and venules are the same in number in the pale and the livid areas; Barker, Hines, and Craig<sup>10</sup> stated that capillaries are more numerous in the livid areas and usually more dilated and with slower blood flow.

From the data available it appears that the best explanation of the mechanism of livedo is as follows: There are areas of maximal blood supply in the skin, perhaps from capillary arborizations from central arterioles which enter the skin from below. In these central areas the tone of the capillaries is slightly greater and the blood flow slightly faster than in the surrounding periphery. Either through organic changes in the blood vessels or through vasospasm of the arteries and arterioles supplying the skin, the capillary atony and stagnation of blood flow in the peripheral areas is further increased. This increase brings about a livid discoloration in annular rings surrounding central pale areas. The discoloration is intensified by exposure to cold, which further increases the vasoconstriction of the arteries and arterioles supplying the skin. The livid areas disappear or change to a pink color with finer reticulation when vascular spasm is released by warming the body of the patient or by sympathetic interruption. Dependency of the affected part similarly brings about some intensification, possibly through the same mechanism, for though there is disagreement on this point<sup>11, 12</sup> it is maintained by some investigators that vasoconstriction occurs when the legs are in a dependent position.<sup>13, 14</sup> The persistence of some

Cleland,<sup>16</sup> believing that the afferent pain fibers from the uterus entered the spinal cord through the eleventh and twelfth spinal roots, injected these roots in five women in labor and obtained analgesia over the lower abdomen and cessation of pain with uterine contractions. Several years previously Dellepiane and Badino<sup>17</sup> had reported alleviation of pain with uterine contractions from a unilateral injection in the region of the third lumbar sympathetic ganglion.

Although lumbar sympathetic anesthesia may ultimately prove of aid in alleviating pain during the first stage of labor, it is my hope that it will not be adopted in general obstetric practice until numerous problems concerned with its use have been thoroughly investigated.

#### SUMMARY

An unusual case of vasospasm of the lower extremities associated with livedo reticularis is presented and the mechanism of livedo is discussed. Lumbar sympathectomy gave an excellent result and appears to be indicated in cases of this kind. Because of absence of pain with the uterine contractions of labor in this patient, the possibility of inhibiting painful stimuli from the uterus by interruption of the lumbar sympathetic impulses is being investigated.

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parturition. Four and one-half years previously sympathectomy had been performed elsewhere for Raynaud's disease and scleroderma. The sweating defect would indicate that the operation undoubtedly included resection of both second and third lumbar ganglia. Though it is very difficult to interpret her subjective sensations during labor they merit consideration. At the time of delivery those attending her were not impressed with anything unusual but felt that her labor was very easy. On careful questioning she states that she was having no pain at all when her membranes ruptured spontaneously at 1:30 A.M. while she was lying in bed. She went to the hospital shortly afterward and fleeting uterine contractions were noted by the examiners. She slept soundly without medication until about 6 A.M. By 8 A.M. labor was definitely established. All during the morning she had no sensations with the uterine contractions except an ill-defined feeling within the abdomen of an intermittent tightening and relaxation, not painful, a sensation akin to that experienced when the skin is stretched and then released. In the afternoon she began to have an aching discomfort in the back which was constant and which was not, as well as she can recall, exacerbated during uterine contractions. The feeling of tightness became stronger. At 4:15 she experienced her first severe pain, an agonizing pain as if she were being squeezed. The exact localization is not recalled, but she thinks it was felt over the abdomen as well as in the pelvis. After three or four such pains she was taken to the delivery room and at 4:45 an 1,860 Gm. child was delivered under sodium pentothal anesthesia. It is not possible to say whether this relatively painless first stage was related to the sympathectomy or whether it was a coincidental easy premature labor.

It will be interesting to learn if other women who have undergone bilateral lumbar sympathectomy have any alteration of subjective feelings during labor or whether they have the customary pain. Regardless of whether the absence of pain in my patient was coincidental or the result of her previous sympathectomy, or whether the second patient had diminished pain as the result of her operation, the question of the relation between lumbar sympathetics and uterine pain deserves fuller study. Further study and observation of cases may or may not provide evidence to suggest that bilateral lumbar sympathectomy may be helpful in alleviating painful uterine conditions or that this operation may be advantageously combined with resection of the hypogastric plexus.

The case reported has led me to investigate the effect of sympathetic anesthesia in labor. A sufficient number of cases has been studied to permit me to say that an effectual injection of a local anesthetic solution into the region of the lumbar sympathetic nerves on both sides will alleviate temporarily the abdominal pain associated with uterine contractions apparently without interfering with the frequency or forcefulness of the contractions and without deleterious effect upon fetus or mother. A preliminary report of this study will be published shortly. As far as I know, direct bilateral injection of the lumbar sympathetic nerves has not been used for abolishing the pains of labor. Some years ago

reported an embolectomy of the aorta with death from a renal infarction twenty-six hours after operation. Circulation was good in both legs after the operation until death.

For the most part, the results of embolectomy in the terminal aorta have been poor. In 1932 Pearse<sup>8</sup> made a critical survey of embolectomy of the extremities, including seven embolectomies of his own in six cases. This survey apparently included the 216 cases reported by Key in 1929. As reported by Pearse, there were 282 embolectomies including thirty-four cases of embolism of the abdominal aorta, 131 of the common femoral, and forty of the brachial artery. Pearse states that for an embolectomy to be considered successful, the patient must survive at least a month after the operation. Of Pearse's collected cases, 133, or 48 per cent of the patients, fulfilled this criterion, a fact which should encourage surgeons to continue their efforts.

Etiology in the patient in the case to be reported was essentially the same as it had been in practically all of the previously reported cases. That is, it has its origin as a thrombus which begins in the left heart and from that point is floated into the arterial tree; if it is small enough, of course, its drifting will come to an end beyond the terminal femoral. However, out of 282 cases, as noted by Pearse, thirty-four came to rest at the bifurcation of the aorta, creating a riding embolus. This particular group presents probably the most fatal type of embolectomy, because it is very difficult to approach the terminal aorta without at least a spinal anesthesia, unless the retrograde procedure of Key is used, and, although this may be successful, it is difficult to see that its success in a riding embolus, such as the case to be reported, would be as good as a direct approach, which was followed in this and previous cases.

The original embolectomy of the aorta through incisions in the right and left common iliac of our patient was followed three days subsequently by embolectomy of the right common femoral at its bifurcation into the profunda and ten days later by a supracondylar amputation of the right limb, which revealed an embolus in the popliteal artery.

#### CASE REPORT

The patient was a 24-year old white woman who entered the hospital because of dyspnea, cough, and fever of one week's duration. She had been a known rheumatic since the age of 5 years when she showed manifestation of chorea which lasted for a year. Three years later she developed polyarthritis which necessitated bed rest for two months. At the age of 10 years she had another attack of polyarthritis, and it was at this time that cardiac manifestations were first noted. At the age of 15 years the patient had a third attack of polyarthritis and carditis, and since that time has been on digitalis and limited activity. Dyspnea on exertion has continued despite this medication. For ten days prior to admission the patient had a cough with increase in her dyspnea and, when a temperature of 103° F. appeared, decided to be hospitalized.

Her past history, aside from rheumatic fever, revealed measles, mumps, and chicken pox in childhood, a tonsillectomy at the age of 7 years, and excision of a pilonidal cyst at 18 years of age.

## EMBOLECTOMY FOR RIDING EMBOLUS OF ABDOMINAL AORTA\*

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PROBABLY the first attempt to remove an embolus by arteriotomy was made in 1895 by Ssabanjew,<sup>1</sup> a Russian surgeon, and although he was unsuccessful, post-mortem examination nineteen days after operation showed the suture line in the blood vessel to be free from clots. Following this attempt, several surgeons did arteriotomies but without success. Although also unsuccessful, Trendelenburg's<sup>2</sup> operation for pulmonary embolism performed in 1907 encouraged further attempts in this field. However, all attempts at embolectomy were unsuccessful until Labey's successful embolectomy of the femoral artery, as reported in 1911 by Mosny and Dumont.<sup>3</sup> In the following year, 1912, Alexis Carrell received the Nobel Prize from the King of Sweden for his researches on the suture of the blood vessels and the transplantation of vessels and organs. It was also in this year that Key<sup>4</sup> reported the second successful embolectomy of the femoral artery. The success of this case, the technique employed by Key, and the work of Carrell greatly stimulated the interest of surgeons in Sweden. By the end of 1927 Key<sup>4</sup> was able to collect 216 cases from the literature and hospital reports, 145 of the patients having been operated upon in Sweden. About five years later, Strombeck, Hindmarch, and Sönderberg<sup>5</sup> of Stockholm collected 364 cases of embolism of the arteries of the extremities, all of the patients having been operated upon in Sweden. Since that time there has been an increasing number of reports from the Scandinavian countries and from this country.

In 1929 Burrow and Flint<sup>6</sup> reported an unsuccessful attempt to remove an embolism at the bifurcation of the abdominal aorta by operation. This case was of considerable interest in that the embolectomy was not performed until thirty-six hours after onset, at a time when there was marked evidence of peripheral circulatory impairment such as mottling, loss of pulsation, complete loss of function of the extremities. All of these symptoms disappeared after removal of the embolus through an incision in the terminal aorta, but the patient died twenty-six hours after operation, from cerebral hemorrhage with infarction, as revealed at necropsy. Several cases of embolectomy of the aorta were reported subsequently with the same result, the interval between operation and death varying from a few hours to a few days. In 1931 Mason and Warren<sup>7</sup>

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protruding through the incision. This was gently removed with forceps and found to be about 6 cm. in length. There was a fair quantity and continuous reflux of blood from below this point. The opening in the vessel was closed with interrupted No. 60 oiled silk sutures. A cuff of peritoneum was placed around the incised part of the artery with endothelial side next to the vessel. A small leak of reflux blood necessitated two more interrupted sutures at the point of arterial opening. The right common iliac was then opened at the same level, about  $1\frac{1}{2}$  cm. below the bifurcation. Incision in the vessel was the same length as the one on the left. As the intima was opened, an organized embolus extruded through the opening. This was slowly removed as on the previous side. Examination of the embolus showed that the distal part was apparently missing, and the embolus came out in three pieces. A catheter with suction was applied up the proximal part of the

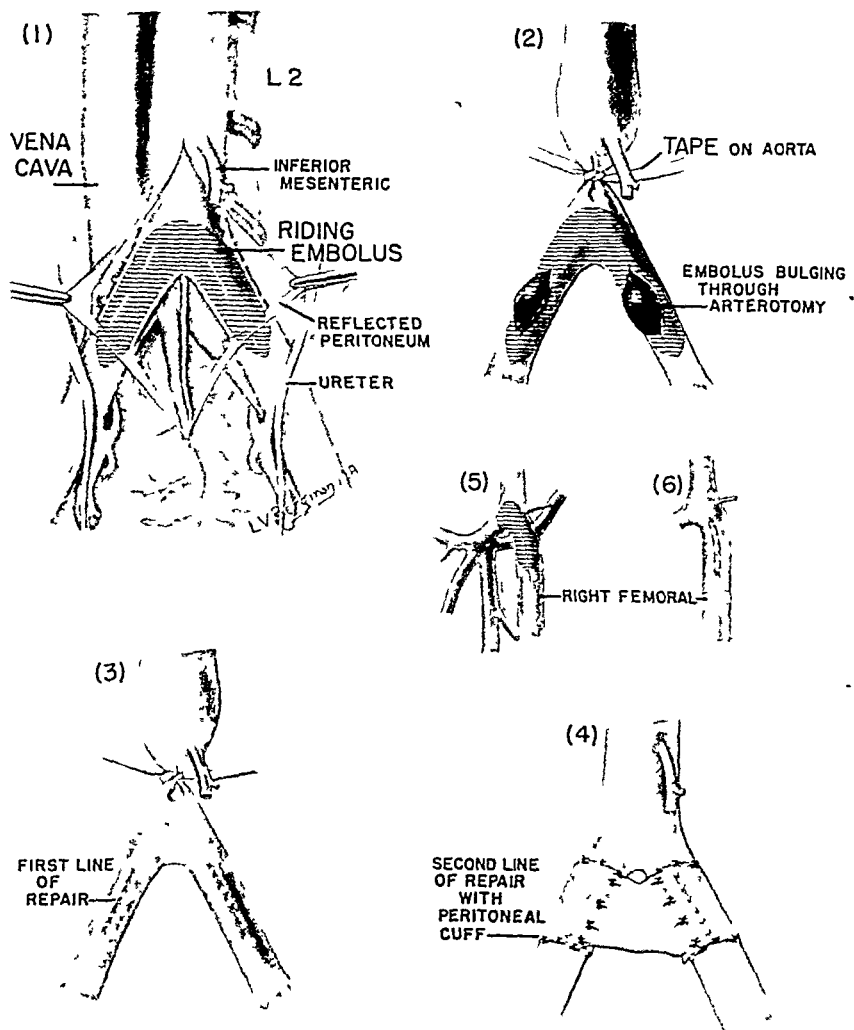


Fig 1—(1) Anatomical exposure. (2) compression of aorta and bilateral arteriotomy. (3) and (4) first and second line of repair—note peritoneal cuff. (5) and (6) femoral arteriotomy with mattress closure after embolectomy.

*Family History.*—Irrelevant.

*Physical Examination.*—On admission physical examination showed a very acutely ill young white female who was feverish and markedly dyspneic and orthopneic. Temperature, 105.6° F., pulse, 150; respirations, 28; blood pressure, 140/82. Eyes: Pupils equal and reactive; fundi normal; no petechiae. Ears, nose, and throat: Nose, engorged turbinates; ears, negative; mouth, tongue furred, teeth poor, pharynx red. Neck: Veins distended and full from below, thyroid slightly enlarged. Breasts: No masses. Chest: Coarse moist rales throughout chest; moderate number of fine crepitant rales at both bases. Heart: Apex beat forceful and present in seventh intercostal space at anterior axillary line, systolic thrill at apex, rapid, irregular in rate with pulse deficit, blowing systolic murmur at apex transmitted upward to ward base, M<sub>1</sub> loud, P<sub>2</sub> accentuated. Abdomen: Liver four fingers below costal margin and tender; spleen and kidneys not felt. Extremities: No edema, clubbing, cyanosis, or petechiae. Neurologic: Physiologic.

*Laboratory Data on Admission.*—White blood cells: 13,150 with 84 per cent polymorphonuclears, 13 per cent lymphocytes, and 3 per cent monocytes. Red blood cells: 4.4 million with 75 per cent hemoglobin (Sahli). Sedimentation Time: Twenty minutes for 18 mm. Urine: Yellow, 1020, acid, one plus albumin; sugar, acetone, and microscopic negative. Wassermann: Negative. Blood Chemistry: Sugar, 117.6 mg. per cent; urea nitrogen, 11.9 mg. per cent. Blood Culture: Negative 1/18, 1/19, 3/20, 1/21, 3/22, 1/30. Sputum: Pneumococcus type 18. Electrocardiogram: Myocardial damage, auricular fibrillation, right deviation electrical axis. Chest Plate: Heart of characteristic mitral configuration, markedly enlarged (cardiothoracic ratio 0.73); lung fields show marked congestion secondary to cardiac decompensation.

*Course.*—The patient was desperately ill on admission to the hospital. It was felt that she had rheumatic heart disease with rapid auricular fibrillation and decompensation and probably bronchopneumonia. She was given 5 cat units of digifolin intravenously, 5 cat units intramuscularly, and later 4 cat units of digitalis leaf orally. Morphine, oxygen, and 50 per cent glucose intravenously were administered. Sodium sulfapyridine, 4 Gm intravenously, were given immediately and sulfathiazole started at 1 Gm. every four hours orally after an initial dose of 3 Gm.

On this regime the patient's improvement was remarkable; her temperature fell to normal, and her fibrillation was well controlled. On the evening of March 28, ten days after admission, she complained of sudden cramplike pains in both legs from the hips down and pain low in the back, followed by a sensation of heat and then numbness. Examination showed both legs from the hips down to be cool, slightly cyanotic, and hypesthetic. Femoral, popliteal, and dorsalis pedis pulses could not be felt, and oscillometric readings were zero. A diagnosis of saddle embolus at the bifurcation of the aorta was made and surgical consultation requested. The diagnosis was confirmed and decision made to operate immediately. Meanwhile, a cradle had been put over both legs with temperature at 90° F., the legs were oiled and bound with cotton, papaverine, 1½ gr., and atropine sulfate, 1/150 gr, were given intravenously; morphine sulfate, 1/6 gr, subcutaneously; papaverine, 1 gr., whiskey, ½ oz., and nicotinic acid, 100 mg. given orally.

She was operated upon four hours following the onset of the pain. Under spinal anesthesia, a midline lower abdominal incision was made. Intestines were pushed back out of the pelvis and above the sacral promontory. The retroperitoneal space was opened and the terminal aorta with its bifurcation exposed. The bifurcation was found at the body of the third lumbar vertebra. About 2 cm. above this level the inferior mesenteric had its origin. There was pulsation down to within 1½ cm. of the bifurcation. No pulsation was noted at the bifurcation or in the right and left common iliaes. The terminal aorta was ligated. Perivascular coats were dissected from the common iliaes. Left common iliac was incised anteriorly for a distance of about 1 cm., and, upon incising the intima, an embolus was noted



protruding through the incision. This was gently removed with forceps and found to be about 6 cm. in length. There was a fair quantity and continuous reflux of blood from below this point. The opening in the vessel was closed with interrupted No. 6-0 oiled silk sutures. A cuff of peritoneum was placed around the incised part of the artery with endothelial side next to the vessel. A small leak of reflux blood necessitated two more interrupted sutures at the point of arterial opening. The right common iliac was then opened at the same level, about  $1\frac{1}{2}$  cm. below the bifurcation. Incision in the vessel was the same length as the one on the left. As the intima was opened, an organized embolus extruded through the opening. This was slowly removed as on the previous side. Examination of the embolus showed that the distal part was apparently missing, and the embolus came out in three pieces. A catheter with suction was applied up the proximal part of the

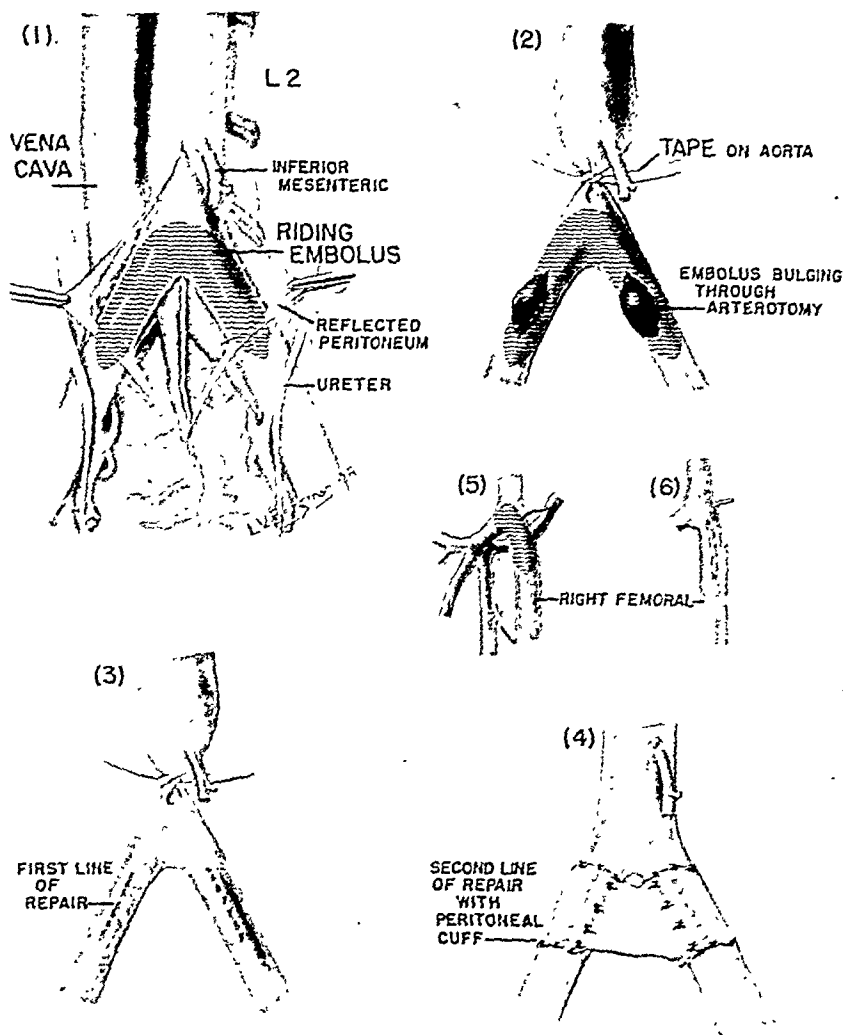


FIG. 1.—(1) Anatomical exposure. (2) compression of aorta and bilateral arteriotomy. (3) and (4) first and second line of repair—note peritoneal cuff; (5) and (6) femoral arteriotomy with mattress closure after embolectomy.

right common iliac, and two or three small pieces of friable embolus were removed from the bifurcation and up to the level of the ligature on the aorta. The catheter with suction was then inserted down into the distal part of the right common iliac for a distance of about 10 to 12 cm., and suction was applied, but no organized embolus could be withdrawn. The opening in the vessel was closed with interrupted No. 6-0 oiled silk. A flap of peritoneum was sutured over the opening in the vessel. It was noted that when the right vessel was opened, there was very little reflux of blood from below. After the opening in the common iliac had been thoroughly closed, the ligature was removed from the terminal aorta. There was no evidence of pulsation below the point at which the terminal aorta had been ligated. The patient's legs and feet were examined at this time, and, although there was definite improvement in the warmth of the left foot and leg, there was no evidence of pulsation in the tibial or femoral arteries. There was slight improvement in the right leg as far as warmth was concerned by the time the operation was completed. The retroperitoneal space opening was closed with continuous atraumatic No. 1. The abdomen was closed in layers.

The patient withstood the operation remarkably well. Additional digitalis was given preoperatively, and the fibrillation was well controlled throughout the operation at a rate below 100 per minute.

The following day the patient's legs were warmer and less cyanotic. Sensation and motor power in the legs improved. The left femoral pulsation was palpable but not the right. Oscillometric readings lower down were still zero. During the course of the next few days the left leg improved even further and an oscillometric reading of  $\frac{1}{2}$  was obtained in the entire leg. The right leg remained cool, pale, and slightly cyanotic. The right femoral pulsation was absent, and no oscillometric reading could be obtained in the right leg. It was decided to explore the right femoral artery and on April 1, three days following the first operation, the patient was taken to the operating room where, under 2 per cent novocain infiltration anesthesia, a transverse incision parallel to the inguinal ligament was made over the *falx inguinale*. Femoral artery was exposed and found to branch at this level into the *profundi* femoral and femoral artery. These arteries were opened separately and a No. 9 catheter inserted for a distance of 40 cm. upward and 40 cm. downward from the point of incision in the vessel. Suction was applied in each instance. The catheter was gradually removed. A small organized embolus was removed from the vessel about  $3\frac{1}{2}$  cm. above its bifurcation. No other emboli could be found. There was a small amount of reflux blood flow with a very weak pulsation following removal of this embolus. The openings in the vessel were closed with two rows of No. 6-0 oiled silk continuous mattress sutures. Skin and fascia were closed in layers with interrupted black silk.

Following this operation, the right thigh became warmer, the color improved, and an oscillometric reading of  $\frac{1}{2}$  was obtained. The portion below the knee remained cool and slightly cyanotic. In addition to the medical therapy previously outlined (intravenous and oral papaverine, whiskey, heat cradle, sedation), a pavex boot was also added.

By April 6 the patient was alert and cheerful and greatly improved. Her left leg was warm and had good femoral pulsation. She could move this leg readily and had no complaints referable to it. The right leg was warm down to the knee but had slightly cool and cyanotic below this point. She could move the leg, but complained of frequent pain in the calf and foot. By April 10, nine days following the femoral exploration, the patient was running a low-grade fever ranging around  $101^{\circ}$  F., and it was obvious that the lower third of the right leg was becoming gangrenous and amputation was decided upon. The following day, under spinal anesthesia, a supra-condylar amputation of the right thigh was performed. Anterior and posterior flap incisions were made through skin, fascia, and muscles. The femoral vein and artery were clamped and cut and the femur was sawed through. The femoral artery was

opened and a No. 9 catheter with suction was applied and fed up into the artery for a distance of about 3 cm. A well-organized embolus about 1.5 cm. in length was removed with a small artery forceps. The artery was then incised for a distance of about 3 cm. and a metal eustachian catheter was inserted for its full length into it. Suction was applied and the catheter gradually removed. There was no pulsation in the vessel, and only a small quantity of arterial blood seemed to come down from it, but in an amount sufficient to necessitate ligating the end of the vessel. The sciatic nerve was retracted downward, injected with absolute alcohol, and about 2 cm. excised. Muscles over the stump of the bone were brought together by interrupted chromic sutures. Skin was closed with interrupted black silk.

Following this operation, the patient rapidly improved and was soon able to get about in a wheel chair. After about a week she started to run a low-grade fever and examination revealed a recurrent infected pilonidal cyst. This was drained (*Bacillus coli*), irrigated, and packed with sulfathiazole. Improvement was noted in the patient's general condition for several days but later began to show more dyspnea and orthopnea than usual. She responded poorly to the usual medical measures. On her twenty-seventh hospital day she was extremely dyspneic, and coarse râles were heard throughout the chest. She responded temporarily to morphine, oxygen, 50 per cent glucose intravenously, and digitalis, but that evening suddenly started to scream, complained of severe pain in the chest, and died within a few minutes.

#### SUMMARY

Although the patient died twenty-seven days postoperatively from what was apparently pulmonary infarction, we feel that the case is of sufficient interest to be reported because it does prove again that patients with severe cardiac conditions can be subjected to major surgical procedures without immediate mortality.

Autopsy would have made the case complete, and we regret that we are not able to give such a report. However, in summary, (1) a case of riding embolus at the bifurcation of the aorta is reported; (2) the patient withstood three major surgical procedures in spite of the fact that she had a severe cardiac condition; and (3) technique of embolectomy has been illustrated.

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# CENTENNIAL OF CRAWFORD LONG'S FIRST USE OF ETHER IN SURGERY

FRANK K. BOLAND, M.D., ATLANTA, GA.

IT HAS been said that medicine has advanced more in the last hundred years than in all other times combined. Such a statement appears to be particularly accurate in the year 1942, since the first surgical anesthetic was administered just one hundred years ago, March 30, 1842. Then followed the epochal pioneer work of Pasteur, Lister, Koch, Roentgen, Halsted, and others, which has contributed so materially toward creating such an unparalleled hundred years in medicine.

Disagreements over priorities in important discoveries in medicine and other sciences have led to discussions and sometimes heated arguments which have never ended and which will not end so long as there is a single supporter to champion the cause of any claimant. In no debate over priority of discovery in medicine has interest and feeling existed so intensely and so long as in the discovery of surgical anesthesia. There seem to be two main reasons for this situation. If the discovery had been an ordinary one the matter would have been settled promptly and forgotten. But since the finding of means to make painless surgery possible was an achievement eagerly desired and sought throughout the centuries, and since no acquisition in medicine was more valuable, it was natural and human that any claimant to the immortal honor would press his demands vigorously, or have them so presented by his advocates. Another reason for the war of words and pamphlets which has existed over the discovery of anesthesia was the fact that all the contestants in the drama played their roles in a period of less than five years. If the different events had been distributed over longer time, and had most of the claimants not known one another and had not been brought into actual contact with one another, the violence of the controversy would have been less marked and sooner forgotten.

It is not the purpose of the present paper to reopen the discussion, but to describe the part taken by one of the participants, Crawford Williamson Long, in commemoration of the centennial of his achievement. As a matter of fact, the name of Crawford Long did not figure conspicuously in the famous "ether controversy." The heated arguments were mainly between the New England contenders and their supporters, Horace Wells, of Hartford, and W. T. G. Morton and Charles T. Jackson, of Boston.

One of the most frequently quoted axioms of Louis Pasteur reads, "In the realm of observation, chance only favors the mind prepared." What preparation had Crawford Long which led him by chance to make such a useful discovery? Many of the world's greatest men have arisen

from the humblest, most unpromising origins. It has been thought by some that Long possessed but little education and training, which was true of most medical practitioners of a century ago. But such was not the case with Dr. Long. Judged by modern standards which require that animal experimentation should precede clinical application in medical studies, Long did not appear to be prepared to produce such a monumental discovery, but he did possess a trained background and keen intellect which enabled him to make careful observations and appreciate their significance.

#### ANCESTRY AND PREPARATION

He was born in Danielsville, Madison County, Georgia, Nov. 1, 1815. His grandfather was Captain Samuel Long, Irish by birth, who emigrated to Pennsylvania in 1762, and settled in Carlisle, marrying Miss Williamson, of Ulster, Ireland. He served in the army of Washington, and at the Yorktown surrender was a captain in the command of the Marquis de Lafayette. After the war, in 1792, Samuel Long moved to Madison County, Georgia, taking with him his 11-year-old son, James, who had been born in Carlisle. This James Long, father of Crawford, married Elizabeth Ware, a Virginia girl, whose parents were born and reared in Albemarle County, Virginia, and had come to Georgia and settled in Madison County. She was an energetic, warm-hearted, ambitious woman, of refined taste and much literary ability. Crawford's father was a planter, and for years was clerk of the Supreme Court. He sat in the state senate for two terms and was the intimate and trusted friend of the Georgia statesman, William H. Crawford, who was successively United States senator, minister to France, secretary of the treasury, and candidate for President of the United States, in 1824, against John Quincy Adams, Andrew Jackson, and Henry Clay. Dr. Long was named after William H. Crawford and Captain Samuel Long's wife.

Crawford attended the academy in his native town, and at the age of 14 years entered Franklin College, now the University of Georgia, where he took the degree of master of arts, in 1835, at the age of 19, being considered "studious and wise" beyond his years, and called "the Baby" at college because of his youth. He stood second in the graduating class. Contemporaneous with him were several distinguished Georgians: General Howell Cobb; General Benning, of Columbus, after whom Fort Benning is named; Senator Herschel V. Johnson; General Francis Bartow, of Savannah, who was killed at the First Battle of Manassas; and Senator A. O. Bacon. His roommate and closest friend, however, was Alexander H. Stephens, who became vice-president of the Confederacy. It is remarkable that two college roommates should have been chosen as the two illustrious citizens to represent Georgia in the National Statuary Hall. Undoubtedly the embryo physician must have received inspiration for his future success by his association with such men as these, as they must have felt the stimulation of contact with him.

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September 22, 1888, at Comfort, Texas, from injuries received in a railroad wreck. She lies buried with her husband in Oconee Hill Cemetery at Athens. Twelve children were born to this marriage; six grew to maturity. The last surviving child, Mrs. Eugenia Long Harper, died July 5, 1940. Two grandchildren are alive, and great- and great-great-grandchildren.

It is interesting to note that for one year, in 1850-51, Dr. Long lived in the budding city of Atlanta, but he found it a rather rough railroad town, with so little promise that he moved to the classic city of Athens, where there were better advantages for educating his children. He continued to reside in Athens until the day of his death, June 16, 1878, after practicing medicine for nearly forty years. A recent writer said that Crawford Long "died in obscurity." Nothing could be further from the truth. When he died the whole state mourned and greater tributes of praise were never showered upon a citizen of Georgia.

#### EMINENT ON MANY COUNTS

Even without being the first to use anesthesia, Dr. Long would be considered one of Georgia's most distinguished physicians. At the unveiling of the monument to his memory in 1912, in Jefferson, Dr. Woods Hutchinson said that Long was in many respects in advance of his day. He treated and cured consumption by food and fresh air, and he treated typhoid fever as it was treated in 1912. He operated several times successfully for cancer of the breast, always clearing the ribs and removing the axillary glands. He is said to have cured several cases of lockjaw and was especially skilled in the use of obstetrical forceps.

Long was reared a Presbyterian, his father and paternal grandfather having been elders in the Presbyterian Church, but he joined the Methodist Church in order to be with his wife. He considered slavery as God's method of civilizing the African, and felt deeply the responsibility of having slaves to control and influence. Politically he was a Whig, and with his friend, Alexander H. Stephens, he opposed secession, but like many other patriots, he "went with his state."

During the War Between the States he did not join the enlisted forces, but was appointed by the Confederate government in charge of the military hospital on the university campus at Athens, where he rendered valuable service. The Southern Cross of Honor was conferred upon him by the United Daughters of the Confederacy.

All who knew him unite in declaring him a man of exceptional qualities of mind and soul. Dignified in manner, his whole appearance betokened culture and high character. He was sensitive, refined, and considerate of others, free from envy, malice, and uncharitableness. He maintained a slight reserve, except among intimates and congenial people. Cheerful in the sick room, he inspired his patients with confidence. He was fond of Shakespeare and good music; he was tall and slender, dressed in conventional black, always with frock coat, usually made by

Long taught for one year in the Danielsville Academy, and after that began the study of medicine at Jefferson, Georgia, under Dr. Grant. He then took a medical course of one year at Transylvania College, at Lexington, Kentucky, which was the second medical school to be organized in this country, Pennsylvania being the first. He reached this distant place by riding horseback over the mountains, with his rifle in his lap, because this section was still infested with Indians who often were on the warpath.

In 1837, he entered the medical department of the University of Pennsylvania, which was then, as today, one of the leading medical schools of the world. Philip Syng Physick, pupil of John Hunter, and father of American surgery, died during Long's first course. William Gibson, pupil of Sir Charles Bell, succeeded Physick as professor of surgery. While traveling in Europe Physick had been present as a spectator at the battle of Waterloo, and was wounded by a stray bullet. He is said to have been the first man to tie the common iliac artery (1812). Nathaniel Chapman was professor of practice of physic and clinical medicine; George B. Wood taught materia medica; William E. Horner, discoverer of the tensor tarsi, was professor of anatomy; Hugh L. Hodge, who invented pessaries and obstetrical forceps, was professor of midwifery; and Robert Hare was the celebrated professor of chemistry. A medical student of this time could hardly have been taught by a more capable faculty.

Receiving the degree of M.D. from Pennsylvania University in 1839, he next went to New York, where he spent eighteen months "walking the hospitals." The extent of postgraduate training offered by this course is not stated, but it was the best that could be obtained in the United States at this period. Among those whom he had opportunity to hear were Valentine Mott, Kearney Rogers, and Willard Parker. From filial duty young Long felt obliged to return home to practice. Had he elected to locate in New York or Philadelphia, as he once decided to do, and could have administered ether for the first time in such a large center, the question of priority in the discovery would not have arisen and have caused such acrimonious discussions.

In 1841, at 26 years of age, Dr. Long settled in the little town of Jefferson, Jackson County, Georgia, buying out the practice of his old preceptor, Dr. Grant. He soon acquired a lucrative practice, which grew rapidly and extended into the neighboring counties and towns of Georgia. His house in the village became the favorite social resort for the young men of the vicinity, and it was here that the discovery of ether anesthesia was made, March 30, 1842.

On August 11, 1842, Dr. Long married Mary Caroline Swain, the 16-year-old daughter of a planter, George Swain, and the niece of Governor Swain, of North Carolina, who was afterward president of the University of North Carolina. She was a lovely and intellectual woman, fit in every way to be the life partner of such a man. Mrs. Long died



assembled at night in the village of Jefferson, Ga., and the party requested me to prepare them some. I informed them that I had not the requisite apparatus for preparing or using the gas, but that I had an article (*sulphuric ether*) which would produce equally exhilarating effects and was as safe. The company was anxious to witness its effects; the ether was produced, and all present in turn, inhaled. They were so much pleased with its effects that they afterwards frequently used it and induced others to use it, and the practice became quite fashionable in the county and some of the contiguous counties. On numerous occasions I inhaled the ether for its exhilarating properties and would frequently at some short time subsequently discover bruises or painful spots on my person which I had no recollection of causing and which I felt satisfied were received while under the influence of ether. I noticed my friends, while etherized, received falls and blows which I believed were sufficient to cause pain on a person not in a state of anesthesia, and on questioning them they uniformly assured me they did not feel the least pain from these accidents.

Observing these facts I was led to believe that anesthesia was produced by the inhalation of ether and that its use would be applicable in surgical operations.

The first person to whom I administered ether in a surgical operation was Mr. James M. Venable, who then resided within two miles of Jefferson, and at the present time in Cobb County, Georgia. Mr. Venable consulted me on several occasions as to the propriety of removing two small tumors on the back part of his neck, but would postpone from time to time having the operation performed from dread of pain. At length I mentioned to him the fact of my receiving bruises while under the influence of the vapor of ether, without suffering, and, as I knew him to be fond of and accustomed to inhale ether, I suggested to him the probability that the operation might be performed without pain, and suggested to him operating while he was under its influence. He consented to have one tumor removed, and the operation was performed the same evening. The ether was given to Mr. Venable on a towel and when fully under its influence, I extirpated the tumor. It was encysted and about one-half an inch in diameter. The patient continued to inhale ether during the time of the operation, and seemed incredulous until the tumor was shown to him. He gave no evidence of pain during the operation and assured me after it was over that he did not experience the least degree of pain from its performance. This operation was performed on March 30, 1842.

The second operation I performed on a patient etherized was on the sixth of June, 1842, and was on the same person for the removal of the other tumor. This operation required more time than the first from the cyst of the tumor having formed adhesions to the adjoining parts. The patient was insensible to pain during the operation until the last attachment of the cyst of the tumor was separated, when he exhibited signs of slight suffering, but asserted, after the operation was over, that the sensation of pain was so slight as scarcely to be perceived. In this operation the inhalation of ether ceased before the first incision was made. Since that time I have invariably desired patients, when practicable, to continue the inhalation during the time of the operation.

Having permitted such a time to elapse without making public my experiments in etherization [the author stated that these operations were made known to physicians and the people all about Jefferson and Athens at the time they occurred], in order to show the correctness of my statements, I procured the certificate of the patient on whom the first operation was performed,

a New York tailor; in short, he was a high-bred, scholarly, Christian gentleman.

#### BEFORE ANESTHESIA

In 1799, Sir Humphrey Davy, the English chemist, announced that the inhalation of nitrous oxide gas would produce insensibility and had cured toothache, adding these significant words, "As nitrous oxide appears capable of destroying pain it may probably be used with advantage during surgical operations." Here he stood upon the very threshold of the wonderful discovery, but Davy was not a medical man, and none was found progressive enough to carry out his suggestion.

Sulphuric ether had been known for a long time as a chemical agent, but it was regarded as too dangerous to be used in medicine. Between the years 1795 and 1839, however, different experimenters, such as Pereira and Faraday in England, Thomson in Scotland, and Godwin, Wood, and others in America, showed that the vapor of ether when inhaled would produce effects similar to those of nitrous oxide gas, such as exhilaration, excitement, laughter, crying, and insensibility, and would relieve the spasmodic disorders of colic, asthma, and whooping cough, and would cause insensibility to pain. And yet no one had the courage to employ ether in surgery or obstetrics. As late as 1839, Velpeau, the famous French surgeon, declared, "To escape pain in surgical operations is a chimera which we are not permitted to look for in our day."

During the first half of the nineteenth century there was an odd class of persons who traveled about the country, first in England and later in the United States, lecturing in public on chemistry. One of the features of the program was to invite certain members of the audience upon the stage to inhale nitrous oxide or ether vapor "for the purpose of provoking exhilaration, excitement, semiconscious gyrations, and mirth-producing antics for the amusement of the spectators." This first began with the use of nitrous oxide, but soon ether became the favorite for the reason that it was more easily manipulated. From these strange entertainments evolved the so-called ether parties, or "frolics," which became popular throughout the country.

Here it is appropriate to insert Dr. Long's own account of how he came to give the first anesthetic for a surgical operation, describing his first cases. This statement was read before the Medical Association of Georgia, in 1852.

#### FIRST OPERATION WITH ETHER

In the Southern Medical and Surgical Journal for December, 1849, I presented an account of what I considered the first use of ether by inhalation as an anesthetic agent in surgical operations; a summary of which I will proceed to read to the Medical Association of Georgia.

Previous to stating the first operation performed by me with ether, I will briefly give the reasons which induced me to make experiments in etherization. In the month of December, 1841, or January, 1842, the subject of the inhalation of nitrous oxide gas was introduced in a company of young men

These were all the surgical operations performed by me in the year 1842 upon patients etherized, no other cases occurring in which I believed the inhalation of ether applicable. Since 1842 I have performed one or more operations, annually, on patients in a state of etherization. I procured some certificates in regard to these operations, but not with the same particularity as in regard to the first operations, my sole object being to establish my claim to priority of discovery of the power of ether to produce anesthesia. However, these certificates can be examined.

The reason which influenced me in not publishing earlier, I was anxious before making my publication to try etherization in a sufficient number of cases to fully satisfy my mind that anesthesia was produced by the ether and was not the effect of the imagination, or owing to any peculiar insusceptibility to pain in the persons experimented on.

At the time I was experimenting with ether, there were physicians "high in authority" who were the advocates of "mesmerism," and recommended the induction of the mesmeric state as adequate to prevent pain in surgical operations. Not withstanding thus sanctioned, I was an unbeliever in the "science," and was of the opinion that if the mesmeric state could be produced at all, it was only on those of strong imagination and weak minds, and was to be ascribed solely to the working of the patient's imagination. Entertaining this opinion, I was the more particular in my experiments in etherization.

Surgical operations are not of frequent occurrence in a country practice, and especially in the practice of a young physician; yet I was fortunate enough to meet with two cases in which I could satisfactorily test the anesthetic powers of ether. From one of these patients I removed three tumors the same day; the inhalation of ether was used only in the second operation and was effectual in preventing pain, while the patient suffered severely from the extirpation of the other two tumors.

In another case I amputated two fingers of a negro boy; the boy being etherized during the operation as to one finger and not during the other—he suffered during the operation as to one finger and not during the other. After fully satisfying myself of the power of ether to produce anesthesia, I was desirous of administering it in a severer surgical operation than any I had performed. In my practice prior to the published account of the use of ether as an anesthetic I had no opportunity of experimenting with it in a capital operation, my cases being confined, with one exception, to excising small tumors and the amputation of fingers and toes. While cautiously experimenting with ether as cases occurred, with the view of testing its anesthetic powers and its applicability to severe as well as minor surgical operations, others, more favorably situated, engaged in similar experiments and consequently the publication of etherization did not "bide my time." I know that I deferred the publication too long to receive any honor from the priority of the discovery, but having by the persuasion of friends presented my claims before the profession, I prefer that its correctness be fully investigated before the medical society. Should the society say that the claim, though well founded, is forfeited by not being presented earlier, I will cheerfully respond: "So mote it be."

Not wishing to intrude upon the time of the association, I have made this short compendium of all the material points stated in my article in the Journal; and if the society wishes any further information on the subject I will cheerfully comply with their wishes.

(Signed) C. W. Long, M.D.

the certificates of two who were present at the time of the operation, and also of his mother, brothers and sisters and a number of his immediate friends who heard him speak of the operations soon after they were performed.



Fig. 1.—Portrait of oil painting of Crawford W. Long by Lewis Gregg.

#### THE FACTS CERTIFIED

The Southern Medical and Surgical Journal of 1849, December, contained but two of the certificates. I have a number of others which may be seen or read, if desired by the association.

My third case was a negro boy who had a disease of the toe which rendered amputation necessary, and the operation was performed July 3 1842, without the boy evincing the slightest degree of pain.

operation having been performed that he would not believe the tumor was removed until it was shown him.

(Signed) E. S. Rawls, M.D.

(Sworn to and subscribed before me this second  
of November, 1853) E. L. Newton, J.J.C.

The opponents of Long's claim to priority in the use of anesthesia say that he kept his discovery a secret and that he, therefore, deserved no credit for it. The next two certificates from Dr. de la Perriere and Dr. Carlton, prominent physicians of the community, show that Long's work was well known to citizens of the town of Jefferson and neighboring places, particularly Athens, the center of learning in Georgia; that it was considered a remarkable discovery by the populace, and that these doctors knew of it and realized its importance:

Georgia, Jackson County.

I, Ange de la Perriere, M.D., do certify that I resided in Jefferson County, Georgia, in the year 1842, and that sometime in that year I heard James M. Venable, then of said county, speak of Dr. C. W. Long's cutting off two tumors from his neck while under the influence of the inhalation of sulphuric ether, without pain or being conscious of the performance of the operation.

I do further certify that the fact of Dr. C. W. Long using sulphuric ether by inhalation to prevent pain in surgical operations was frequently spoken of and notorious to the county of Jackson, Georgia, in the year of 1842.

A. de la Perriere, M.D.

(Sworn to and subscribed before me this thirtieth  
of March, 1854) N. H. Pendergrass, J.P.

Athens, Clarke Co., Georgia.

I, the undersigned, do certify that in May, 1843, I assisted Dr. R. D. Moore in amputating the leg of a colored boy Augustus, then the property of Mr. Wm. Stroud, who resided in this county; and that I distinctly recollect hearing Dr. R. D. Moore say, "If I had thought of it before leaving home I would have tried Dr. C. W. Long's great discovery, namely the administration of sulphuric ether as an anesthetic in performing the operation." Having neglected to bring the ether, Dr. Moore finally concluded to influence the patient with morphia; under which influence the operation was performed.

Jos. B. Carlton, M.D.

Many other certificates could be offered to prove these facts but these seem sufficient for the present narrative. The original copies of all the documents, affidavits, etc., are now in possession of the Smithsonian Institute, in Washington, D. C. Many distinguished surgeons and other writers have contributed articles on Long's discovery of anesthesia. Among these are J. Marion Sims, Hugh H. Young, John Chalmers da Costa, Dudley W. Buxton, the English anesthetist, Joseph Jacobs, Long's young office boy, and others. The most complete account is given in Mrs. Taylor's work.

If the statements of Crawford Long's daughters are authentic, his use of anesthesia in obstetrics preceded by two years its employment by Sir James Y. Simpson. Mrs. Harper, in a signed letter to the writer,

## FURTHER PROOFS

Following the reading of the foregoing paper the Association (See Transactions, pp. 113-117) unanimously passed the following resolution:

Resolved, That this society is of the opinion that Dr. Crawford W. Long was the first person who used sulphuric ether as an anesthetic in operations, and as an act of justice to him individually and to the honor of the profession of our own state, we most earnestly recommend him to present at once his claims to priority in the use of this most important agent to the consideration of the American Medical Association at its next meeting, Dr. Dickinson, Dr. Cooper, Dr. S. N. Harris, committee.

Mr. Venable's story of the first anesthetic is given in the following affidavit:

I, James M. Venable, of the county of Cobb and state of Georgia, on oath depose and say, that in 1842 I resided at my mother's in Jackson County, about two miles from the village of Jefferson, and attended the village academy that year.

In the early part of the year the young men of Jefferson and the country adjoining were in the habit of inhaling ether for its exhilarating powers, and I inhaled it frequently for that purpose, and was very fond of its use.

While attending the academy I was frequently in the office of Dr. C. W. Long, and having two tumors on the back of my neck, I several times spoke to him about the propriety of cutting them out, but postponed the operation from time to time. On one occasion we had some conversation about the probability that the tumors might be cut out while I was under the influence of sulphuric ether, without my experiencing pain, and he proposed operating on me while under its influence.

I agreed to have one tumor cut out and had the operation performed that evening after school was dismissed. This was in the early part of the spring of 1842.

I commenced inhaling the ether before the operation was commenced and continued it until the operation was over. I did not believe the tumor was removed until it was shown to me.

A month or two after this time, Dr. C. W. Long cut out the other tumor, situated on the same side of my neck. In this operation I did not feel the least pain until the last cut was made, when I felt a little pain. In this operation I stopped inhaling the ether before the operation was finished.

I inhaled the ether in both cases, from a towel, which was the common method of taking it.

James M. Venable.

(Sworn to before me) Alfred Manes, J.P.

This operation was done in the presence of four witnesses, James E. Hayes, A. T. Thurmond, W. H. Thurmond, principal of the academy, and Edmond S. Rawls, the last of whom testifies as follows.

I, Edmond S. Rawls, of Rome, Floyd Co., Ga., on oath depose and say that—on one occasion during that year (1842) I was present with James M. Venable in the office of Dr. C. W. Long, in Jefferson, Jackson Co., Ga., and witnessed Dr. C. W. Long cut out a tumor from the side of neck of J. M. Venable while said Venable was fully under the effects of the vapor sulphuric ether inhaled from a towel, and without his exhibiting the least symptoms of suffering pain from the operation. J. M. Venable was so unconscious of the

until December, 1849, three years after the universal publication and adoption of the method. While it is true that Long did not publish his work in a periodical until this date, from the very first he made no secret of the discovery; he always operated in the presence of witnesses, and encouraged publicity by public discussion and by urging the use of ether by other physicians, so that it was known over a wide section of country. The nearest hospital, medical journal, and railroad were at Augusta, 140 miles away, and the nearest newspaper, a weekly, was at Athens, 20 miles away.

Crawford Long has been honored in many ways besides those already mentioned. Various bodies of medical men have adopted resolutions expressing the belief that he is entitled to be called the discoverer of anesthesia. The Southern Medical Association passed such a resolution in 1922. In 1878, Marion Sims presented the state of Georgia with a heroic size oil painting to be hung in the State Capitol. In 1912, the University of Pennsylvania unveiled a medallion to perpetuate the memory of its illustrious alumnus. The same year Dr. (afterwards Governor) L. G. Hardman, of Commerce, Georgia, gave to the town of Jefferson a marble shaft commemorating the deed of its former citizen, and in 1921, a reduplication of the beautiful medallion at the University of Pennsylvania was placed on the campus of the University of Georgia by Dr. Joseph Jacobs, an alumnus of the institution.

The best portrait of Long is the one painted by Lewis Gregg for Alumni Hall at the University of Georgia. The state of Georgia has erected at Danielsville, Long's birthplace, a replica of the statue in Statuary Hall. In 1931, the name of the Davis-Fischer Sanitarium was changed to the Crawford Long Memorial Hospital, the largest private hospital in Atlanta. Every year on March 30, exercises commemorate the discovery of anesthesia as "Crawford Long Day" at the University of Georgia. In 1940, the United States Post Office issued a postage stamp bearing a portrait of Dr. Long. The first sale of this stamp was made the occasion of a memorable celebration at Jefferson, Georgia, April 8, 1940, when Postmaster General James A. Farley presented the first sheet of stamps to Mrs. Eugenia Long Harper, Dr. Long's sole surviving child. On the Centennial day of Long's discovery, March 30, 1942, an admirable play based on the subject was presented in Atlanta and later given in Augusta at the meeting of the Medical Association of Georgia.

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declared that she and other members of the family had often heard their mother say that Dr. Long administered ether to her at the birth of her second child, who was Mrs. Frances Long Taylor, born Dec. 17, 1845. The family Bible corroborates this date. This important date in the history of anesthesia was not published until after Mrs. Taylor's death. She could have given it as an addition to her father's claim to fame, but in so doing she would divulge her age, which the proud lady was loath to do.



Fig. 2.—Long's first operation under ether. Maurice Siegler

It has been charged that Long used ether anesthesia only a few times and then abandoned it. In a letter written in 1921, Mrs. Taylor stated that the complete records of her father's operations under ether were lost in 1908, but that at the time she wrote there were living witnesses or their descendents in and around Athens who testified that Dr. Long used ether continuously up to the very day of his death. From memory Mrs. Taylor named fifteen occasions in which ether was employed as an anesthetic, five times in difficult obstetrical cases. The other ten cases included eight breast amputations, one amputation of the leg, and an operation for cancer of the groin. In the breast amputations it is claimed that the axillary glands were removed and the ribs "scraped." Mrs. Taylor also wrote that there were many "minor" operations under ether anesthesia which were not recorded.

The chief argument used against Crawford Long as the discoverer of surgical anesthesia is that he made no publication of his experiments



The average age is 40.2 years with 47.3 per cent occurring between the ages of 20 and 40 and 47.3 per cent occurring after the age of 40. Two cases were under 20 years of age. This in itself tends to segregate the condition from the more common condition of multiple diverticulosis and diverticulitis of the colon which occurs almost exclusively after the age of 40.

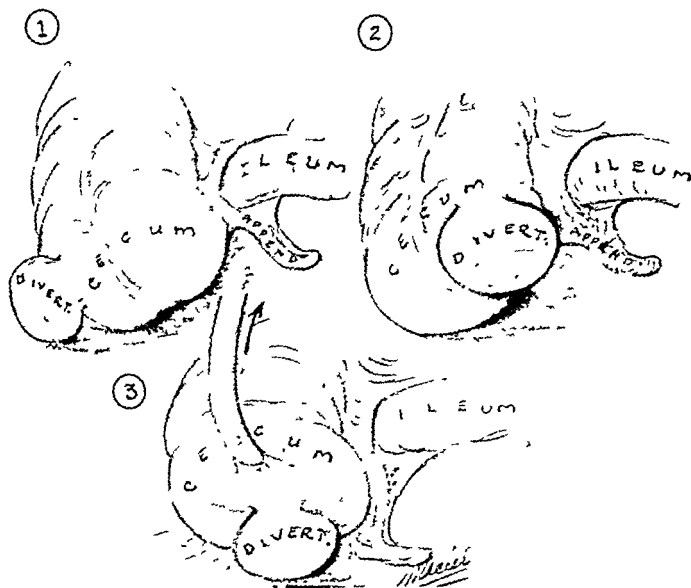


Fig. 1.—The three most common locations of solitary diverticula of the cecum.

The history obtained from a patient with acute diverticulitis of the cecum is very often a typical history for acute appendicitis. Thirty-one and five-tenths per cent of the cases gave a story of epigastric or generalized abdominal pain at the onset with subsequent localization in the right lower quadrant. The duration of pain prior to admission was twenty-four hours or less in 31.5 per cent of the cases, while 55.2 per cent gave a history of pain from one to three days in duration. The patients in 100 per cent of the cases complained of right lower quadrant pain, usually cramping in character. Patients in 44.7 per cent of the cases complained of nausea, while in 26.3 per cent of the cases, vomiting was present.

Examination of the abdomen revealed right lower quadrant tenderness to be present in 97.3 per cent of the cases with associated muscle spasm in 81.5 per cent. A right lower quadrant mass was detected in 26.3 per cent of the patients. The temperatures varied from 98.6 to 102° F., with an average of 99.6. White blood count varied from 6,000 to 22,500 with an average of 12,700. Patients in 23.6 per cent of the cases gave a history of one or more previous attacks.

## ACUTE DIVERTICULITIS OF THE CECUM

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**D**URING the past several years we have encountered six cases of acute diverticulitis of the cecum. In reviewing the literature one is amazed to find so few reported cases of the condition. The first case was reported by Patier in 1912, and since then only thirty-one additional cases have appeared in the literature. It is also surprising to find that the standard textbooks of surgery do not mention the condition.

A complete statistical review of the reported cases has not appeared in the literature to date. Because of the marked similarity in the clinical pictures of appendicitis and diverticulitis of the cecum, the apparent difficulty in recognizing the condition at the operating table, and the lack of standardization in treatment of the condition, we felt that a complete analytical study of the disease was indicated.

Diverticula occur throughout the gastrointestinal tract and are found most frequently in the colon. Diverticula of the colon are classified as the true or congenital and the false or acquired types. The congenital or true type is probably a developmental anomaly falling into the same class as a Meckel's diverticulum. The wall of the true diverticulum contains all the layers of the normal intestinal coat. The false or acquired diverticulum is believed by most writers to be formed as a result of a localized area of weakness in the intestinal wall, combined with a tendency toward constipation and an increased intracolonic pressure. The false diverticula show the absence of one or more muscular layers. True diverticula are almost always found in the region of the cecum and are characteristically single. (See Fig. 1.) False diverticula are almost always multiple and are found most frequently in the rectosigmoid region; they show a decreased incidence from left to right. Both the true and the false diverticula are often asymptomatic, but with the onset of acute inflammation they give rise to acute abdominal signs and symptoms. Thus, true solitary diverticula of the cecum may give rise to acute signs and symptoms in the right lower quadrant.

The thirty-two reported cases of acute diverticulitis of the cecum, together with the six cases treated in our clinic make up the series for the study in this communication. We realize the number of cases is necessarily small but we do feel that a statistical study of the series does bring out several pertinent points.

Acute diverticulitis of the cecum occurs with almost equal frequency in the two sexes with 57.8 per cent of the cases present in females.

diagnosed clinically and treated conservatively. The patient made an uncomplicated recovery and the cecal diverticulum was revealed in a follow-up barium enema. The tissue was studied in those cases in which an excision and closure or resection was done and all the specimens showed an acute inflammation in the wall of the diverticulum. Some contained fecaliths but many did not. Follow-up barium enemas were done in thirteen of the cases. Nine of the cases showed normal colons; two showed the diverticulum of the cecum and two showed multiple diverticula of the left colon.

In this series of thirty-eight cases there were two deaths, giving a mortality rate of 5.26 per cent, which is much better than one would expect when thirteen of the cases were subjected to a radical resection and anastomoses. One of the deaths occurred in a patient who was subjected to a resection and anastomosis. The other death occurred in one of the patients in whom only drainage had been instituted.

#### CASE REPORTS

CASE 1.—D. G., a 59 year old white man was admitted to the hospital, on April 5, 1929. Eight hours before admission the patient developed cramping right lower quadrant pain which persisted and increased in severity. He had no nausea or vomiting and his bowels moved normally the day of the onset. No history of previous similar attacks was obtained.

Positive findings on examination were limited to the abdomen. There was moderate right lower quadrant tenderness with no muscle spasm or rebound tenderness. No mass was palpable. Rectal examination was not recorded; temperature was 98.6° F.; W. B. C., 9,800; urine, negative. The preoperative diagnosis was acute appendicitis.

The patient was explored through a McBurney incision and the cecum was found involved with a hard indurated mass. The lesion was diagnosed as a carcinoma of the cecum. A right rectus incision was made and a right colectomy and ileotransverse colostomy was performed. The patient made an uneventful recovery. Pathologic studies of the specimen revealed the lesion to be an acutely inflamed diverticulum of the cecum with an associated typhlitis. No evidence of carcinoma was found in the sections.

CASE 2.—A white man, aged 30 years, was admitted to the hospital on Oct. 25, 1937. Two weeks before admission this patient had an attack of upper abdominal pain associated with nausea. The attack lasted only two hours and was not associated with right lower quadrant pain or vomiting. Four days before admission the patient developed a similar crampy upper abdominal pain which the night before admission shifted to the right lower quadrant. Nausea was present but the patient did not vomit. He was somewhat constipated and took a cathartic the day before admission. The patient denied any previous similar attacks.

Examination revealed nothing remarkable other than the abdominal and rectal findings. There was slight fullness in the right lower quadrant with a suggestion of a mass in the right iliac fossa. Tenderness was moderate in the right lower quadrant associated with some spasm. In addition there was definite rebound tenderness and pain on coughing both referred to the right lower quadrant. Rectal examination revealed moderate tenderness high on the right; W. B. C., 18,500, urine negative; and temperature, 98.6° F. The preoperative diagnosis was acute appendicitis.

A preoperative diagnosis of acute appendicitis was made in 68.4 per cent of the cases. This is, of course, the logical diagnosis in a patient with such a history and such clinical findings. A comparison of the pertinent points in the history and findings in acute diverticulitis of the cecum to those in appendicitis as compiled by Reid, Poer, and Merrell reveals the striking similarity of the clinical picture in the two conditions (Table I). In one case the correct diagnosis of acute diverticulitis of the cecum was made before operation. A diagnosis of appendiceal abscess was made in four cases and the remainder of the diagnoses included intestinal obstruction, abscess of unknown etiology, etc. In none of the cases was a diagnosis of carcinoma of the cecum made preoperatively.

TABLE I

COMPARISON OF THE FINDINGS IN ACUTE DIVERTICULITIS OF THE CECUM  
AND ACUTE APPENDICITIS

	ACUTE APPENDICITIS	ACUTE DIVERTICULITIS
Sex	66% Male	57.8% Female
Age 11 to 30 inclusive	68%	2 under 40 47.3% (20-40) 47.3% over 40
Typical history of acute appendicitis	53%	31.5%
Nausea	78%	44.7%
Vomiting	73%	26.3%
Pain	94%	100.0%
W.B.C. (Average)	17,200	12,700
Temperature (Average)	100.0° F.	99.6° F.

The diagnosis of the condition at the operating table with the pathology exposed is often quite difficult. In 63.4 per cent of the cases the condition was recognized after the abdomen had been opened.

Five of the cases were diagnosed carcinoma of the cecum; three, tuberculosis of the cecum; two, benign ulcer of the cecum, and in three the interpretation of the lesion at the operating table was not recorded. The lesion is most frequently located on the lateral and anterior aspect of the cecum, but did occur on the medial or posterior aspect of the cecum as well. The condition often develops into a large, firm, indurated mass involving the cecum, which does appear not unlike a malignant lesion. This similarity to carcinoma in gross appearance at least partly explains the high percentage of cases in which radical methods of treatment were used. Patients in 34.2 per cent of the 37 cases operated upon had a right colectomy and ileocolostomy performed upon them. Subsequent pathologic studies of the specimens revealed an inflamed diverticulum of the cecum with an associated typhlitis and pericecal inflammatory mass.

In 52.6 per cent of the cases the condition was recognized and an excision of the diverticulum was done. In three cases the condition was recognized but left undisturbed and an appendectomy was done. In one case drainage only was done. In one instance the condition was

He was seen one month later and was free of symptoms. A follow-up barium enema revealed a normal colon.

CASE 5.—M. D., a white woman, 66 years of age, was admitted to the hospital on July 12, 1940, complaining of abdominal pain. Twenty-four hours before admission the patient developed a cramping right lower quadrant pain which persisted and gradually increased in severity. There was associated anorexia but no nausea or vomiting. The day of the onset the patient noted constipation and she had no bowel movement the day of admission. She had had a similar attack three years before.

Examination revealed a blood pressure of 160/90. There were occasional coarse rhonchi throughout the lung fields. The abdomen was obese and there was diffuse tenderness and muscle spasm in the right lower quadrant. No mass was palpable and there was no rebound tenderness. Pelvic and rectal examinations revealed no masses or tenderness. Temperature was 100.0° F.; W.B.C., 9,500; urine showed 1+ albumin. The preoperative diagnosis was acute appendicitis.

The patient was explored through a McBurney incision and the cecum was found involved in an inflamed mass of omentum and fibrinous adhesions. A pericecal abscess was found which was drained with cigarette drains and the wound was closed loosely. The appendix appeared normal and thus was not disturbed.

The patient had a stormy postoperative course, developing cardiac asthma and pneumonia. In spite of all supportive therapy she died on the fourteenth postoperative day.

An autopsy was obtained, which revealed the inflammatory process in the diverticulum and surrounding cecum to have subsided completely. The death was attributed to a bilateral pneumonia and cardiac failure.

CASE 6.—W. H., a white man, aged 47 years, was admitted to the hospital on April 4, 1941, with a complaint of abdominal pain. Twenty-eight hours before admission he noted for the first time a generalized abdominal pain in both lower quadrants which became localized to the right lower quadrant eight hours before admission. He complained of no nausea or vomiting and his bowels had moved normally. The patient denied any previous similar attacks.

The positive findings on examination were limited to the abdomen, which was normal in contour. There was moderate tenderness and slight muscle spasm in the right lower quadrant, fairly well localized to McBurney's region. There was also local and referred rebound tenderness to that region. No mass was palpable and peristalsis was active. Rectal examination was negative; temperature, 99.0° F.; W.B.C., 12,700; and urine negative. The preoperative diagnosis was acute appendicitis.

The patient was operated upon through a McBurney incision and an acutely inflamed diverticulum was found on the lateral wall of the cecum. A normal appendix was found which was removed. The diverticulum was left undisturbed and the McBurney incision was closed without drainage. The patient's postoperative course was uneventful and he was discharged from the hospital free of symptoms and in good condition. A follow-up barium enema was not done.

#### COMMENT

Concerning the treatment of acute cecal diverticulitis it is obvious that a resection and anastomosis is an unnecessary radical procedure which is done as a result of a mistake in diagnosis at the operating table. One must admit that recognition of the condition is often very difficult but there are several definite aids in making the diagnosis.

The patient was operated upon through a McBurney incision and on the anterior cecal wall 3 cm. above the ileocecal junction an indurated, inflammatory mass 2 by 2½ cm. was found. The mass was carefully dissected free from the bowel until a small neck was exposed which communicated with the lumen of the bowel. The mass was excised and the remaining defect was closed with purse-string sutures. The appendix was removed. The inverted area of the cecal wall was marsupialized and a protective wick was placed down to the area and the wound closed loosely. Pathologic studies revealed an acute inflammatory reaction in the wall of the diverticulum.

The patient's postoperative course was uneventful and he was discharged on his thirteenth postoperative day. He was seen in the follow-up clinic and was entirely symptom free. A checkup barium enema was negative.

CASE 3.—H. D., a white man, aged 31 years, was admitted to the hospital Dec. 4, 1937. He gave a history of a vague left abdominal pain beginning twenty-four hours previously. The pain tended to subside and he slept well the night before admission, but when he awoke the next morning he had a catching right lower quadrant pain. The pain was exaggerated by walking and straightening up. He was nauseated but did not vomit and gave a history of constipation preceding the attack. A cathartic was taken the morning of admission and his bowels moved twice without exaggeration of the pain. There was no history of previous attacks.

Physical examination revealed slight injection of nasal mucous membranes and slight redness of the pharynx. The abdomen was of normal contour. There was moderate tenderness in the right lower quadrant without muscle spasm. No rebound tenderness or masses were found and the rectal examination was negative. Temperature was 99.6° F.; W. B. C., 15,200; urine completely negative.

The preoperative diagnosis of acute appendicitis and acute pharyngitis and coryza was made.

The patient was operated upon through a McBurney incision and 2 cm. above the appendix on the anterior cecal wall an inflamed, indurated mass 1½ cm. in diameter was found. The neck was dissected out, ligated, the mass excised, and the stump inverted with a purse-string suture. The appendix was also removed. Pathologic studies of the specimen revealed the lesion to be an acutely inflamed diverticulum of the cecum with an associated typhilitis.

Postoperatively the patient did very well and was discharged on the tenth postoperative day. He was seen in the follow-up clinic two months later and was free of symptoms. A checkup barium enema was done, which was entirely negative.

CASE 4.—H. G., a colored man, aged 29 years, was admitted to the hospital on July 19, 1938. He gave a history of the onset of acute upper abdominal pain twenty-four hours previously, which subsided. Seven hours before admission a cramping right lower quadrant pain appeared, which persisted and increased in severity. The pain was increased by coughing and by movement. There was no associated nausea, vomiting, or constipation. The patient denied any previous similar attacks.

Positive findings on examination were limited to the abdomen. The abdomen was normal in contour. There was moderate tenderness and muscle spasm in the right lower quadrant most marked just lateral to McBurney's point. Definite local and referred rebound tenderness to the area mentioned was present. Peristalsis was normal; rectal examination, negative; temperature, 99.4° F.; W.B.C., 12,700; and urine, negative. The preoperative diagnosis was acute appendicitis.

The patient was operated upon and an acutely inflamed diverticulum was found on the posterior wall of the cecum. The diverticulum was excised and the defect closed. In addition, a normal appendix was removed. The McBurney wound was closed without drainage and the patient made an uneventful recovery. Pathologic studies revealed an acute inflammatory reaction in the wall of the diverticulum.

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The majority of the cases occur in patients under the age of 40 and give a fairly characteristic history which closely simulates the history of acute appendicitis. One-third of the patients have had previous attacks. In those cases which have developed large inflammatory masses palpation of the cecal wall adjacent to the mass through the opposing wall frequently reveals the mouth of the diverticulum which establishes the diagnosis. In many of the cases the reaction is not so extensive and the acutely inflamed diverticulum is easily recognized. However, even in the simple acutely inflamed diverticula there is usually an associated indurated inflammatory reaction in the adjacent cecal wall. This makes the excision of these lesions difficult and the closure of the defect very difficult and usually insecure. The technical difficulty encountered in removing these lesions and obtaining a secure closure together with the definite tendency for them to drain into the bowel and subside makes us feel that surgical removal either by the radical procedure or by local excision is definitely contraindicated in most cases.

#### CONCLUSIONS

1. Acute diverticulitis of the cecum is a condition which cannot be differentiated clinically from acute appendicitis and as a result must occasionally be coped with when operating for acute appendicitis.

2. In the majority of cases, symptoms developed in the patients, under 40 years of age.

3. Diverticula of the cecum are characteristically solitary diverticula and are of the true type.

4. When acutely inflamed they show varying degrees of reaction from a simple acutely inflamed cecal out-pouching to the development of a large indurated inflammatory cecal and pericecal mass.

5. Acute diverticulitis of the cecum should be considered in any patient with acute right lower quadrant symptoms and signs, who previously has had an appendectomy.

6. If a clinical diagnosis of the condition can be made conservative, treatment along with chemotherapy should be instituted.

7. A radical excision of the mass by resection and anastomosis is definitely not indicated. A local excision and closure of the defect in most cases is probably not advisable. Except in those cases which have developed an abscess and in which drainage is indicated, the abdomen should be closed without doing an appendectomy and without drainage, and chemotherapy should be instituted. This is particularly true when an open mouth to the diverticulum can be palpated.

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# SYNOVIAL SARCOMA WITH REPORT OF TWO CASES

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## HISTORICAL

THE subject of synovial sarcoma abounds in discrepancies and presents a great deal of confusion, particularly when reviewing the literature pertaining to this group of tumors. For example, in reading the bibliographies accompanying monographs dealing with synovial sarcomas, one is struck with the varying histologic standards employed in tabulating the reported cases. As far back as 1894, Salter and Hardie reported a case of primary sarcoma of the synovial membrane of the knee joint in a 25-year-old male patient, and designated the tumor a spindle-cell sarcoma. Yet, this case is rarely referred to in the more recent bibliographies dealing with this subject. The same holds true in the case of Lockwood reported in the Transactions of the London Surgical Society in 1902 under the histologic diagnosis of spindle-cell sarcoma, and the one by Turner in the same year which was designated mixed-cell sarcoma involving the synovial membrane of the ankle joint.

As one commences a review of this group of malignant tumors involving the extremities, one is at first startled to learn what an exceedingly small percentage of cases it comprises. Yet, a more careful study of the literature leads one to suspect that the paucity of available case reports is more apparent than real.

To explain this discrepancy, one must remember that synovial membranes of joints, bursae and tendons consist of a lining stratum composed of specialized connective tissue cells and an underlying layer of fibrocytes. It is quite possible that the variation in histologic features presented may, in a great measure, be due to the point of origin of the tumor in the synovial membrane. Thus, a tumor arising directly from the lining stratum will present the characteristic features of clefts lined with characteristic polyhedral cells, which have been so ably described by Knox, Berger, and DeSanto and associates. On the other hand, a tumor arising from the deep fibrocytic layer will probably present spindle cell characteristics, thereby accounting for the designation of spindle-cell sarcoma of synovial membrane. Another possible explanation of the divergence of designations attributed to these tumors as a result of varying histologic features may be that, as a result of metaplastic changes occurring in the tumor cells by virtue of their location in joints, bursae and tendon sheaths, the cells may take on forms somewhat different from those originally presented, and thus give rise to the variation in nomenclature. Whatever the case may be, it appears

that the disease is far more prevalent than one is led to believe by a casual survey of the existing literature.

The earliest reported case of synovial sarcoma, according to Knox, was that of v. Ruediger Rydygier in 1906, which concerned a tumor involving the knee joint in a 20-year-old girl. A personal survey of the literature, however, disclosed the fact that as far back as 1894, Salter and Hardie reported a case of spindle-cell sarcoma of the synovial membrane of the left knee joint in a 25-year-old male patient. Antedating the report of Rydygier by four years are two case reports, one by Lockwood, which he designated spindle-cell sarcoma, involving the synovia of the right knee, and the other by Turner called mixed-cell sarcoma of the synovia of the ankle joint. In 1910, Lejars and Rubens-Duval presented the first real compilation of cases of synovial tumors. Because of the perivascular grouping of cells, Faccini, in 1923, reported a case and employed the term sarcomatous perithelioma to describe the tumor. The designation synovioma was given to this group of tumors by Smith, in 1927.

In 1931, Dietz reviewed the literature which comprised ten cases, and added one of his own. The first reported case of synovial sarcoma to appear in the American literature was one reported by Wagner in 1930.

A comprehensive treatise dealing with pathologic entities involving the joints was presented by Sabrazes and his associates in 1932, in which the subject of synovial sarcoma was thoroughly and adequately discussed. In 1936, Knox reviewed the literature and added three cases of her own. Her discussion of the histopathology of the disease was instrumental in placing this group of tumors upon a sounder and firmer pathologic basis than heretofore.

Coley and Pierson, in 1937, reported a group of fifteen cases of synovioma collected from the records of the Memorial Hospital. One year later, Berger reported five additional cases and critically analyzed the existing literature and pointed out that several of the cases reported as synovial sarcomas such as those of Ruediger Rydygier, Hannemuller, the third case reported by Knox, the cases of Faccini, Tavernier, Hodgson and Bishop, and Fievez were really doubtful in that they failed to meet his critical requirements.

#### ETIOLOGY

Out of a total of 76 collected cases, including the two here reported, a history of trauma was definitely present in 19, an incidence of 25 per cent, too small to signify a causal relationship. DeSanto and associates believe that a large number of these tumors occur in and around the knee joint, thereby suggesting a possible relationship between chronic bursitis and synovitis and synovial sarcoma. The incidence of tumors involving the knee joint and its surroundings as tabulated in this series is 48.7 per cent.

Sex plays an insignificant role in this disease. There were 42 cases among men as against 33 in women. In one instance the sex was not mentioned.

Of the 74 cases where the age was mentioned, 46 patients were between 20 and 40 years of age, an incidence of 62.1 per cent. Beyond 40 there were 21 patients (28.4 per cent), and 7 patients were under 20 (9.5 per cent). The oldest reported case was that of a woman 75 years of age, while the youngest was an infant 9 months old. The average age incidence in the entire group was slightly over 33 years, which is distinctly less than one sees in the group of sarcomas involving fascia and bone.

The most recent monograph fully dealing with this subject was by DeSanto and his associates, in 1941, in which 16 personally observed cases were reported. Snyder reported a case of synovium of the knee joint in a woman, in 1942, and Briggs presented 9 additional cases in 1942.

#### PATHOLOGY

Synovial sarcomas originate primarily in synovial tissue, and for this reason are found in joints, bursae and tendon sheaths. In view of the fact that the synovial lining of bursae situated around joints is frequently in direct communication with the synovium lining the adjacent part, it is at times impossible to state with certainty whether a synovial sarcoma situated in the vicinity of a joint has had its origin within the joint or in the bursa adjoining the joint, making tabulation on the question of location somewhat uncertain.

Synovial tumors may be classified as circumscribed, diffuse, and encapsulated. Circumscribed tumors are frequently found in tendon sheaths and bursae. The diffuse variety usually occurs in and around the knee joint and involves the popliteal space and the region above the patella. Encapsulated tumors are usually situated within para-articular bursae.

In general, it may be stated that on gross appearance these tumors are soft and myxomatous, although it is not unusual to find some which are firm and tough. Areas of brownish pigmentation scattered throughout the growth, due to the presence of old blood, are frequently seen. One may also find islands of calcification, bone, and cartilage within tumors.

#### HISTOPATHOLOGY

The histologic identification of synovial sarcomas is far more difficult than the recognition of other types of sarcomas, and to be conclusive, multiple sections are frequently required. A characteristic feature of such tumors is the presence of spaces or clefts which occasionally contain mucin or blood. The clefts are lined by strands of tissue composed of polyhedral or cuboidal cells often resembling pavement epithelium. Interspersed among these cells one sees areas composed of

closely packed flat and spindle-shaped cells. Both types of cells usually show mitotic figures. The histiocytic features of these tumors are manifested in a variety of characteristic manners. The cells may have large single round or ovoid nuclei and heavy reticulated cytoplasm arranged in strands with little or no evidence of clefts. On the other hand, the cells may be multinucleated, giving the impression of giant-cell sarcomas. Because of the presence of large xanthoma cells in some synovial sarcomas, these tumors may be mistaken for benign giant-cell xanthomas. Unless specimens are taken from various parts of the growth, a section may be obtained with cellular architecture indistinguishable from neuro- or fibrosarcoma. The presence of calcium, bone, and cartilage has been reported in synovial sarcomas. Knox points out that one of the characteristic features of this type of tumor is the presence of swollen cells which result from mucoid degeneration. True mucus has never been found in these tumors.

#### SYMPTOMATOLOGY

Pain was present in 40 of the 76 reported cases, an incidence of 52.6 per cent. It was a prominent symptom in cases where the tumor involved the knee joint, but was either absent or insignificant in the encapsulated or circumscribed variety.

A tumor was noted in 71 of the 76 cases (93.4 per cent), and was present for an average duration of 30 months. Where the tumor occupied a superficial position as the cubital fossa, olecranon region, or wrist, it was discovered early, while tumors within the confines of the knee joint, or deeply imbedded in the popliteal space, escaped detection until well advanced. The average duration of symptoms was 36 months, ranging from 1 month up to 10 years.

A survey of the 76 collected cases, including the two about to be reported, reveals the fact that the tumor involved the knee joint, including the popliteal space, in 37 patients (48.7 per cent). The elbow joint, including the antecubital fossa, was involved in 8 instances (10.5 per cent), the ankle joint in 7 (9.2 per cent), the foot in 6 (8 per cent), the thigh in 5 (6.6 per cent), and the palm of the hand 3 times (4 per cent). The wrist joint was involved twice (2.6 per cent) as were the fingers also. The space above Poupert's ligament, axilla, forearm tendon sheath, flexor brevis tendon, dorsum of hand and toe were each involved once (1.3 per cent).

#### PROGNOSIS

For general purposes it may be stated that all synovial sarcomas are malignant to a greater or lesser degree. Those tumors presenting a greater number of multinucleated giant cells are believed to possess less malignant tendencies, yet out of 4 such cases described by DeSanto and his co-workers, 2 promptly recurred after extirpation. One of these has been reported well after 3 years, following 2 local resections.

The most malignant type consists of tumors characterized by closely approximated cells presenting oval or round nuclei. Such tumors, following removal, quickly metastasize to the lungs and bones. Tumors presenting well-defined clefts and cells resembling most the characteristics of synovial cells occupy a position between the two extremes above noted. Knox estimated the interval between the time the patients were first observed and the time of their terminal illness as varying between 7 months and 7½ years.

A survey of the reported cases shows that in the majority of instances, treatment was promptly followed by recurrence and metastases (56.6 per cent). In 13 cases reported by DeSanto and associates, in which local excision was carried out, prompt recurrence took place in 10 of them within 9 months, one patient developed axillary metastases, and the remaining 2 were reported well after 9 and 14 months, respectively.

These same authors reported 7 cases treated by delayed amputation, of which 6 sarcomas were in the knee joint and 1 in the flexor tendon of the ring finger. Only 2 patients, of this group survived, 1 being alive after 22 months, and the other after 1 year.

They recommend wide local excision for the encapsulated and accessible tumors, reserving radical amputation for those tumors which, on histologic study, show a high degree of malignancy, and in cases where local recurrence follows resection. Radical amputation is immediately indicated in all diffuse and inaccessible tumors. Deep roentgen therapy may be of some use as an adjuvant to surgery.

#### CASE REPORTS

CASE 1.—B. M., aged 30 years, a porter and single, was first seen by us on Oct. 5, 1940, complaining of a small swelling on the palm of the right hand of three years' duration. The family and past histories were negative. He had never had a venereal disease. On close questioning, he thought that he might have traumatized his hand in carrying luggage. Nine months previously a physician had incised this swelling. There was no loss of weight, nor any other symptoms, save for a tendency to tire easily on exertion. The wound did not feel tender, nor give rise to pain.

Physical examination, save for the lesion on the palm of the right hand, was essentially negative. Examination of the right palm disclosed a deep linear wound along the thenar palmar fold, in the proximal end of which there was a shallow opening with a necrotic base which bled easily on palpation. A probe could not be introduced into the deep tissues. Lymphadenopathy was absent at this time.

Roentgenologic examination of the lungs revealed no evidence of metastases. Hemoglobin was 89 per cent.

Superficial x-ray exposures to the right palm were given during the next 3 months. In spite of local dressings with sulfanilamide powder alternating with urea crystals, improvement was not noted. At this time examination disclosed a palpable epitrochlear node in the right arm. The local lesion could best be described as a deep jagged wound extending into the thenar crease of the right palm with a necrotic grayish base. Biopsy revealed the presence of synovial sarcoma.

On Feb. 14, 1941, extirpation of the growth was carried out under cyclopropane anesthesia.

*Pathologic Report* (Dr. Arthur Schiffrin).—The specimen consists of several fragments of tissue removed from different parts of the palm, received fixed in formalin.

*Microscopic:* (1) Sections from deep palmar fascia area: The fragments are infiltrated by tumor tissue. In some areas the latter form the lining of small cleft-like spaces. This lining is of irregular thickness and in some sites forms small moundlike eminences which project into the lumina of the cleftlike spaces. The cells vary in size and shape. Those closest to the lumen are often larger, more polygonal, and with better defined cell outlines. Their cytoplasm is pale and nuclei are of moderate size, elliptical or round. Some of the nuclei are larger and somewhat lobulated, while others show atypism. Rare ones show mitoses. These cell layers are intermingled with and in continuity with cells which are more numerous in the deeper portions and are definitely smaller, flatter, more spindle shaped, and more closely knitted together. They fuse with the subjacent collagenous connective tissue so that no basement membrane to this entire lining layer can be demonstrated. Scattered and dense collections of round cells are present in the deeper and adjacent portions. The tumor infiltration extends into adjacent fibrous and fatty tissue.

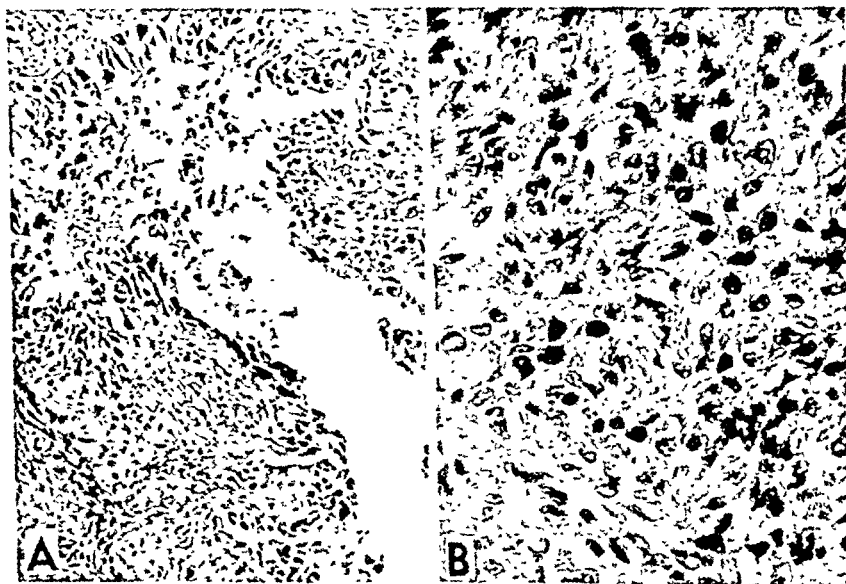


Fig. 1 (Case 1).—A, Low-power view showing cleftlike space, lined by imbricated epithelial-like cells. B, High-power view showing polygonal, globoid, and pale cells in continuity with spindle-shaped cells; several mitoses and atypical nuclei are seen.

(2) Sections were also taken from nerves, lumbrical muscles, and skin at the resected edge of the operative area. No infiltration was present. Sections taken through the main mass leading down to the deep palmar fascia area showed cleft-like spaces lined by polygonal epithelial-like cells as already described. The skin adjacent to the mass showed tumor infiltration.

*Diagnosis:* The diagnosis was synovial sarcoma showing infiltration of subcutaneous tissue, fibrous tissue, and fat. The nerve and deeper muscle tissues are not infiltrated.

Radical amputation was refused. Up to the present there has been no recurrence, and the patient is apparently well.

CASE 2.—A. M., a 47-year-old married woman, an artist, was first seen on April 11, 1940, complaining of a painless swelling of the right knee of 10 days' duration, swelling of the ankles, and occasional swelling of the eyelids. There was no history of trauma.

Physical examination was essentially negative. No abnormality was noted around the knee joint.

She was again seen on Oct. 7, 1940, complaining of puffiness around both knees, more marked around the right. At this time examination disclosed a fluctuant swelling on the inner aspect of the right knee which was aspirated, yielding about 30 c.c. of bloodstained fluid. Specimens of the fluid were sent to the laboratory for culture and for microscopic examination of centrifuged sediment for cells. These were reported negative. From that time to Dec. 12, 1940, aspirations were carried out on several occasions, and amounts of fluid varying from 9 to 50 c.c. were removed. X-ray taken on Dec. 19, 1940, failed to show any involvement of bone. On Jan. 13, 1941, 95 c.c. of fluid were aspirated from the right knee, and 2 c.c. of quinine and urethane were injected, and after 5 injections at weekly intervals, the knee appeared normal. Following an examination on April 3, 1941, the patient went on vacation and returned November 13, complaining of swelling and soreness around the right knee. X-ray examination at this time revealed a fusiform elastic swelling arising from the soft parts of the inner aspect of the right knee above the inner condyle of the femur.



Fig. 2 (Case 2).—A, Low-power view showing cleftlike space lined by a broad zone of cellular tissue whose outermost layer contains epithelial-like, pale, polygonal, and globular imbricated cells. B, Higher power showing nests of solid syncytial and polygonal cells with regular and atypical nuclei; mitoses are present.

Operation was performed Dec. 11, 1941. Situated beneath the lower fibers of the vastus internus muscle of the thigh, just below the inner aspect of the knee, there was a tumor about the size of a small peach, containing considerable old blood and necrotic tissue. This very closely resembled necrotic papillomatous tissue so frequently found in cases of papillary carcinoma of the bladder. The capsule of the tumor was thickened and adherent to the muscle fibers of the vastus internus.

Radical local excision of this mass was carried out and the wound healed by primary union in 6 days. Three weeks later another and wider dissection was carried out at the Memorial Hospital, followed by deep x-ray treatments. The patient refused amputation. At present she is confined to the hospital with diffuse metastases to the abdomen and lymph nodes.

*Pathologic Report* (Dr. Arthur Schiffrin).—

*Macroscopic.*—The specimen consists of numerous fragments of tissue. Many portions consist of fibrotic friable tissue. Several broad fragments show a delimiting outer fibrotic wall with no penetration by its contents. The internal surface of these fragments is irregular, rough, shaggy, and friable, and contains papillary elevations of hemorrhagic material which in some places is canary yellow and in other places brownish in color.

*Microscopic:* The wall of the main lumen is irregular and numerous irregular polypoid elevations project from it. These elevations consist of tumor tissue infiltrating the wall. The tumor tissue includes very cellular areas which contain large cells varying from polygonal cells to cells with large protoplasmic processes and syncytial cytoplasm. The nuclei vary from regular large vesicular nuclei containing distinct nucleoli, to small dark and dense, and often large irregular, bizarre atypical nuclei. Multinucleated cells are present and both regular and irregular types of mitoses are present.

Where the tumor tissue borders a lumen or a cleft, the outermost zone shows a multicellular layer of paler, more succulent cells having a membranous-like appearance. This is in direct continuity with subjacent cells which have a more fibroblastic appearance. Within the cellular areas there are areas of necrosis, interstitial hemorrhage, numerous xanthoma cells, and hemosiderin laden cells. The cytoplasm of the membranous-like portion varies from eosinophilic and granular to pale and clear.

At one site a blood vessel within the capsule shows subintimal tumor-cell infiltration. Where the tissue is quite cellular there are lumina which are possibly artefacts, but there are definite cleftlike lumina which are obviously not artefacts.

*Diagnosis:* Synovial sarcoma with marked infiltration of the bursal wall.

#### SUMMARY AND CONCLUSIONS

Synovial sarcoma is a highly malignant tumor arising from synovial membranes of joints, bursae and tendon sheaths. The paucity of case reports of tumors of this type is more apparent than real because of the variance in designations under which they have been recorded. This discrepancy in designation is due to the variation in histologic architecture of the tumor, depending upon the site or origin of the tumor from the various layers of the synovial membrane. Thus, a tumor originating from the lining stratum of the synovial membrane will present certain characteristic features, while one arising from the deep fibrocytic layer will present features closely simulating the ordinary spindle-cell sarcoma. Furthermore, variations in nomenclature may also occur as a result of metaplastic changes occurring in the tumor cells by virtue of their location. Although some tumors are firm and tough, the majority are soft and myxomatous. A characteristic feature of synovial sarcoma is the presence of clefts lined by strands of polyhedral or cuboidal cells resembling pavement epithelium. Areas composed of closely packed, flat or spindle-shaped cells are often interspersed among these strands of cuboidal cells. Large xanthoma



TABLE I  
REPORTED CASES OF SYNOVIAL SARCOMA

AUTHOR	AGE (YEARS)	SEX	LOCATION	HISTORY OF PRE-EXISTING TRAUMA OR INFECTION	OUTSTANDING SYMPTOMS			PRE- OPERATIVE DIAGNOSIS	TREATMENT	END RESULTS
					PAIN	TUMOR OR SWELLING	DURATION			
Salter and Hardie, 1894	25	Male	Knee joint	Not given	Positive	Positive	5 yr.	Spindle-cell sarcoma	Local excision fol- lowed by amputa- tion	Well 6 mo. later
Lockwood, 1902	24	Female	Knee	None	Positive	Positive	3 yr.	Spindle-cell sarcoma	Local excision	Died 11 hr. after op- eration
Turner, 1902	28	Male	Ankle	Knocked foot against brass rail	Positive	Positive	2 mo.	Mixed-cell sarcoma	Local excision	Not given
v. Ruediger Rydygier, 1906	20	Female	Left knee	Not given	None	Positive	?	?	Resection of joint tumor	Patient reported well after 11 mo.
Hamemul- ler, 1909	44	Male	Ankle joint	Not given	Not given	Not given	Not given	Sarcoma	Biopsy followed by local extirpation	?
Lejars and Rubens- Duval, 1910	22	Male	Left knee	None	Positive	Positive	3 yr.	Rheumatism	Removal of tumor from intra-articu- lar surface, fol- lowed by amputa- tion	Not given
Chenot and Tzanek, 1912	38	Female	Left astrag- aloseph- oid joint	None	Positive	Positive	8 mo.	None	Local extirpation	Not given
Faccini, 1923	38	Male	Knee	Not given	Not given	Not given	Not given	Not given	Not given	Not given
Smith, 1927	?	?	Inner aspect of thigh near Hun- ter's canal	Not given	Not given	Not given	Not given	Not given	Operation (type not given)	Died 6 mo. after op- eration of pulmo- nary metastases

Idem	21	Female	Space above Poupart's ligament	Not given	Positive	Positive	4 mo.	Not given	X-ray	Died with metastases
Idem	35	Male	Knee	Not given	None	Positive	5 mo.	Not given	Local excision followed by delayed amputation	Metastases
Wegelin, 1928	28	Male	Outside of left patella	None	None	Positive	?	Not given	Excision	Patient well 5 mo. later
Tavernier, 1930	23	Female	Knee	Not given	Positive	Positive	Several yr.	Periostitis	Excision followed by recurrence and a secondary resection of knee joint	?
Prym, 1930	66	Female	Knee	Not given	?	Positive	7 yr.	Tuberculous arthritis	Local operations followed by amputation	Died in 1 yr. after amputation
Dietz, 1931	Not given	Female	Knee	Injury 5 years previously	?	Positive	5 yr.	Not given	Local removal	Not given
Sabrazes et al., 1932	18	Female	Left knee	Not given	Positive	Positive	5 yr.	Popliteal cyst or abscess, then tuberculous	Local excision followed later by amputation	Died 10 yr. after onset of symptoms and 8 mo. after amputation with pulmonary metastases
Cooperman, 1932	21	Female	Flexor brevis tendon	Patient had fallen from a ladder	?	Positive	Not given	Not given	Local excision	Well 8 mo. later
Bono and Collet, 1935	25	Female	Outside knee joint	Not given	Not given	Not given	Not given	Not given	Not given	Not given
Hodgson and Bishop, 1935	28	Male	Knee joint	Injury to knee 1 year previously	Positive	Positive	7 yr.	Not given	X-ray as prescribed	Death in 1 yr. with metastases in skin and thigh 7 mo. after onset

TABLE I  
REPORTED CASES OF SYNOVIAL SARCOMA

AUTHOR	AGE (YEARS)	SEX	LOCATION	HISTORY OF PRE-EXISTING TRAUMA OR INFECTION	OUTSTANDING SYMPTOMS			PRE- OPERATIVE DIAGNOSIS	TREATMENT	END RESULTS
					PAIN	TUMOR OR SWELLING	DURATION			
Salter and Hardie, 1894	25	Male	Knee joint	Not given	Positive	Positive	5 yr.	Spindle-cell sarcoma	Local excision fol- lowed by amputa- tion	Well 6 mo. later
Lockwood, 1902	24	Female	Knee	None	Positive	Positive	3 yr.	Spindle-cell sarcoma	Local excision	Died 11 hr. after op- eration
Turner, 1902	28	Male	Ankle	Knocked foot against brass rail	Positive	Positive	2 mo.	Mixed-cell sarcoma	Local excision	Not given
v. Ruediger Rydygier, 1905	20	Female	Left knee	Not given	None	Positive	?	?	Resection of joint tumor	Patient reported well after 11 mo.
Hannemul- ler, 1909	44	Male	Ankle joint	Not given	Not given	Not given	Not given	Sarcoma	Biopsy followed by local extirpation	?
Lejars and Rubens- Duval, 1910	22	Male	Left knee	None	Positive	Positive	3 yr.	Rheumatism	Removal of tumor from intra-articu- lar surface, fol- lowed by amputa- tion	Not given
Chenot and Tzanck, 1912	38	Female	Left astrag- aloscaph- oid joint	None	Positive	Positive	8 mo.	None	Local extirpation	Not given
Faccini, 1923	33	Male	Knee	Not given	Not given	Not given	Not given	Not given	Not given	Not given
Smith, 1927	?	?	Inner aspect of thigh near Hun- ter's canal	Not given	Not given	Not given	Not given	Not given	Operation (type not given)	Died 6 mo. after op- eration of pulmo- nary metastases

Berger, 1938	30	Male	Thigh	None	None	Positive	?	Not given	Local excision	Recurrence after 5 mo.
Idem	38	Male	Thigh	None given	None	Positive	6 mo.	Not given	Local excision	Recurrence with inguinal, abdominal, and pulmonary metastases, and death in 5 mo.
Idem	26	Male	Axilla	None given	None	Positive	3 mo.	Lympho-sarcoma	Local excision	Died 2 yr. after onset of tumor with most likely pulmonary metastases
Idem	75	Female	Wrist, adherent to tendon sheath	None given	None	Positive	7 yr.	Not given	Local excision with recurrence in 3 weeks; amputation 7 months later	Not given
Idem	50	Male	Thigh	None given	None	Positive	1 yr.	Not given	Local removal	No follow-up (considered by Berger as a malignant xanthomatous giant-cell tumor)
Brunner, 1936	47	Male	Bursa bicipital space	None given	?	Positive	7 yr.	Adamantinoma	Local removal followed by metastases in 2 months; then local removal and x-ray as prescribed	Axillary recurrence 6 mo. after second removal; death with cerebral metastases 10 yr. after onset
Salazar et al., 1932	50	Male	Elbow	None given	?	Positive	5 yr.	Malignant synovium	Local removal	Died shortly after, probably from pulmonary metastases
Coley and Pierson, 1937	45	Male	Index finger	Continual injury of finger in course of work as cabinet maker	None	Positive	7 mo.	Not given	Excision followed by recurrence, followed by x-ray as prescribed	Tumor continues to grow; no further information

TABLE I—CONT'D

AUTHOR	AGE (YEARS)	SEX	LOCATION	HISTORY OF PRE-EXISTING TRAUMA OR INFECTION	OUTSTANDING SYMPTOMS			PRE- OPERATIVE DIAGNOSIS	TREATMENT	END RESULTS
					PAIN	TUMOR OR SWELLING	DURATION			
Zwahlen, 1935	22	Female	Forearm tendon sheath	None	Positive	Positive	Several yr.	Tuberculous synovitis	X-ray as pre- scribed, biopsy followed by ampu- tation	Death 8 yr. after on- set of symptoms and 2 yr. after am- putation
Idem	16	Male	External malleolus	None	None	Positive	?	?	Local excision fol- lowed in 4 years by amputation	Died 3 mo. after am- putation with pul- monary and pleural metastases
Fievez, 1935	59	Female	Left ankle joint	Injury 7 years pre- viously	Positive	Positive	7 yr.	?	Amputation 10 years after tumor appeared	Not recorded
Knox, 1936	22	Female	Elbow	None	Positive	Positive	3 yr.	Spindle-cell sarcoma	Local removal 18 months after tu- mor appeared, fol- lowed by amputa- tion	Died 10 yr. after first symptoms, pleural and pulmo- nary metastases
Idem	33	Male	Popliteal space	None	Positive	Positive	6 mo.	Not given	Amputation	Died of pulmonary metastases about 2 yr. after amputation
Idem	24	Male	Foot	Struck foot 2½ years previously	Positive	Positive	2½ yr.	Hemangi- oma or sar- coma	Local excision fol- lowed by amputa- tion	4 yr. after amputa- tion patient had pulmonary metas- tases
Black, 1936	36	Male	Palmar as- pect of web of thumb	Crushing in- jury to soft tissues between thumb and forefinger 3 years previously	None	Positive	3 yr.	Not given	Local excision	No recurrence after 6 mo.; believes this tumor benign

Idem	27	Male	Palm	Injury of right palm, with laceration 9 months previously	Positive	Positive	9 mo.	Not given	Excision followed by recurrence, then x-ray as prescribed	Tumor still present 16 mo. later
Idem	16	Female	Knee	None	Positive	Positive	6 mo.	Not given	Local excision followed by recurrence, followed by wide excision, and removal of patella plus x-ray as prescribed	Apparently well 28 mo. after prescribed x-ray
Idem	45	Female	Large toe	None	Positive	Positive	1 mo.	Not given	Excision followed by recurrence and further excision plus x-ray as prescribed	Well 5½ yr. later
Idem	45	Male	Knee	None	None	Positive	3 yr.	Not given	Excision followed by recurrence	1 year later recurrence; amputation advised
Idem	29	Female	Popliteal space	None	Positive	Positive	9 yr.	Not given	Local excision followed by recurrence and excision	Died of pulmonary metastases 9 yr. after onset of symptoms
Idem	44	Female	Dorsum of foot	None	None	Positive	1 yr.	Not given	X-ray as prescribed	No change in patient's condition
DeSanto et al., 1941	30	Male	Antecubital fossa	Not given	None	Positive	6 mo.	Fibrosarcoma	Local excision plus x-ray as prescribed	Alive with axillary metastases after 14 mo.
Idem	63	Male	Elbow	Not given	None	Positive	2 yr.	Not given	Local excision	Alive and apparently well after 11 mo.
Idem	50	Female	Elbow (olecranon bursa)	Not given	Positive	Positive	10 yr.	Olecranon bursitis	Local excision; re-fused amputation; recurrence	Recurrence 6 mo.

TABLE I—CONT'D

AUTHOR	AGE (YEARS)	SEX	LOCATION	HISTORY OF PRE-EXISTING TRAUMA OR INFECTION	OUTSTANDING SYMPTOMS			PRE- OPERATIVE DIAGNOSIS	TREATMENT	END RESULTS
					PAIN	TUMOR OR SWELLING	DURATION			
Idem	9 months	Male	Knee	Not given	None	Positive	7 mo.	Not given	Excision followed by recurrence, then x-ray as pre- scribed	No recurrence after 3½ yr.
Idem	24	Male	Foot	Not given	Positive	Positive	10 mo.	Not given	Local excision fol- lowed by recur- rence	Died of pulmonary metastases 2½ yr. after onset of symptoms
Idem	34	Male	Plantar as- pect of foot	Not given	Positive	Positive	3 yr.	Not given	X-ray as prescribed followed by ampu- tation	Died of pulmonary metastases 4 yr. after onset of symp- toms
Idem	22	Female	Dorsum of hand	Trauma to hand 7 years pre- viously	None	Positive	7 yr.	Not given	Local excision fol- lowed by recur- rence, then ampu- tation	Died of pulmonary metastases 4 yr. after onset of symp- toms and 15 mo. after amputation
Idem	47	Male	Knee	Trauma to knee 4 months be- fore tumor appeared	Positive	Positive	2 yr.	None given	Excision followed by x-ray as pre- scribed, and then amputation	Died of pulmonary metastases 3 yr. after onset of symp- toms
Idem	35	Female	Knee	Trauma 8 years pre- viously	Positive	Positive	8 yr.	None given	Local excision fol- lowed by x-ray	Well 2 yr. later
Idem	12	Female	Knee	Not given	Positive	Positive	1 yr.	None given	Local excision fol- lowed by x-ray and amputation	Well 6 yr. after op- eration
Idem	64	Male	Foot	Not given	Not given	Positive	5 mo.	Not given	Local excision fol- lowed by amputa- tion	Well 3½ yr. later

Idem	32	Female	Flexor tendon of ring finger	None	Positive	Positive	Few mo.	Dupuytren's contracture	Local excision, deep x-ray as prescribed and radium, followed by delayed amputation	Well 19 mo. after amputation
Idem	48	Male	Popliteal space	None	None	Positive	1 mo.	Not given	2 local excisions	Well 2 yr. later
Idem	46	Male	Popliteal space	None	Positive	Positive	1 mo.	Cyst of popliteal space	Local excision, synovectomy, and amputation	Well 1 yr. after amputation
Idem	45	Male	Antecubital fossa	None	Positive	Positive	10 dn.	Not given	Local excision plus x-ray as prescribed	Died of generalized metastases in 7 mo.
Idem	40	Male	Knee	None	None	Positive	2 yr.	Fibrosarcoma	Excision and x-ray as prescribed	Died of pulmonary metastases in 18 mo.
Wagner, 1930	35	Male	Knee joint	None	None	Positive	10 yr.	Chronic synovitis	Repeated local excisions, deep x-ray as prescribed and delayed amputation	Died of pulmonary metastases 10 yr. after amputation
Snyder, 1942	35	Female	Left knee	Followed an attack of sinusitis	Positive	Positive	2 yr.	Angioma	Local excision followed by amputation and x-ray as prescribed	Well 18 mo. later
Briggs, 1942	17	Female	Right ankle	Injury to right ankle 4 months previously (mild blow)	None	Positive	4 mo.	Not given	Excision and x-ray as prescribed	Recurrence 1 yr. later with inguinal metastases; death from pulmonary metastases 5 yr. later
Idem	45	Female	Head of left fibula	None	Positive	Positive	4 yr.	Not given	Excision and x-ray as prescribed	Living and well with no recurrence 7 yr. later
Idem	30	Female	Left foot	None	Positive	Positive	2 1/2 yr.	Simple benign cyst	Excision and x-ray as prescribed	Recurrence 2 yr. later, followed by amputation; death from pulmonary metastases 1 yr. after amputation



TABLE I—CONT'D

AUTHOR	AGE (YEARS)	SEX	LOCATION	HISTORY OF PRE-EXISTING TRAUMA OR INFECTION	OUTSTANDING SYMPTOMS			PRE- OPERATIVE DIAGNOSIS	TREATMENT	END RESULTS
					PAIN	TUMOR OR SWELLING	DURATION			
Idem	26	Female	Thigh	Not given	Positive	Positive	9 mo.	Not given	Local excision, x-ray as prescribed; recurrence	No further data
Idem	23	Male	Knee joint	Hit knee joint shortly before onset of symptoms	Positive	Positive	18 mo.	Chronic traumatic synovitis	Amputation plus Coley's serum	Died 13 mo. after amputation with pulmonary metastases
Idem	22	Male	Knee (bur- sa?)	Spiked on lateral aspect of knee 3 years previously	Positive	Positive	3 yr.	Not given	Local excision followed by recurrence in 3 months, and then excision; refused amputation	No recurrence after 1 yr.
Idem	37	Female	Knee joint	Wrenched knee 2½ years previously	Positive	None	2½ yr.	Internal derangement of knee joint	Amputation	Alive with pulmonary metastases after 2½ yr.
Idem	24	Male	Knee joint	Injury of knee after falling down a flight of stairs	Positive	Positive	6 yr.	Calcified popliteal cyst	Local excision, deep x-ray, and delayed amputation	Died of pulmonary metastases 2½ yr. after amputation
Idem	34	Female	Wrist region	None	None	Positive	6 yr.	Not given	Local excision	No recurrence in 9 mo.
Idem	25	Male	Knee joint	?	Positive	Positive	6 to 8 yr.	Traumatic arthritis and possible ruptured meniscus	2 local excisions and delayed amputation	Died of pulmonary metastases 10 mo. after amputation

cells are occasionally seen, which may lead to the erroneous diagnosis of benign giant-cell xanthoma. According to Knox, one of the characteristic features of this type of tumor is the presence of swollen cells which result from mucoid degeneration, although mucus has never been found in these tumors.

A careful review of the literature discloses the presence of 76 recorded cases, including two of ours which are presented here. Of this number, there was a history of trauma in 19 (25 per cent). Forty-six of the 76 patients were between the ages of 20 and 40 (62.1 per cent). Pain was present in 52.6 per cent of patients, but when the tumor involved the knee joint it was a prominent symptom. A tumor was noted in 93.4 per cent of cases and was present for an average duration of 30 months. The average duration of symptoms was 36 months. The knee joint was involved in 48.7 per cent of cases, the elbow in 10.5 per cent, and the ankle in 9.2 per cent, while the palm of the hand was involved in only 4 per cent of the cases.

The prognosis is poor. The least malignant tumors are supposedly those containing a greater number of multinucleated cells, while those characterized by closely approximated cells presenting oval or round nuclei display the highest degree of malignancy. Tumors presenting well-defined clefts and cells resembling most the characteristics of synovial cells occupy a position between these two extremes.

A survey of the reported cases shows that in 56.6 per cent prompt recurrence and metastases followed treatment. According to Knox, the interval between the time of onset of symptoms to the time of the terminal illness varied between 7 months and 7½ years. In our tabulated series of 76 cases, there were follow-ups on 64 patients, and of this number, 10 (16 per cent) were found to be living 5 years or more, while 9 (14 per cent) were alive between 3 and 5 years. Eight patients (13 per cent) succumbed between the first and third years, and 15 (24 per cent) died within the first year. Twenty-one persons (33 per cent) were reported well without further comment.

Local wide excision is advocated for the encapsulated and accessible tumors. Radical amputation is reserved for tumors showing, on histologic examination, a high grade of malignancy, or where local recurrence followed extirpation, and also in inaccessible tumors. Irradiation is advocated only as an adjuvant to surgical intervention.

Two cases of synovial sarcoma are here presented, one involving the palm of the hand, and the other the knee joint.

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TABLE I—CONT'D

AUTHOR	AGE (YEARS)	SEX	LOCATION	HISTORY OF PRE EXISTING TRAUMA OR INFECTION	OUTSTANDING SYMPTOMS			PRE- OPERATIVE DIAGNOSIS	TREATMENT	END RESULTS
					PAIN	TUMOR OR SWELLING	DURATION			
Idem	22	Female	Left ankle	Injury by falling and striking left ankle 2½ years previously	None	Positive	2½ yr.	Not given	Excision and x-ray as prescribed	No recurrence 18 mo. following operation
Idem	15	Male	Left knee	None	Positive	Positive	3 yr.	Fascial sar- coma	Mid-thigh amputa- tion	Living and well 4 yr. after operation
Idem	17	Male	Left elbow	None	None	Positive	4 mo.	Benign cyst	Excision and x-ray as prescribed fol- lowed by second excision 1 year later	Living and well 7 yr. later
Idem	15	Female	Right knee	Outer sur- face of right knee struck 7 years pre- viously	Positive	Positive	7 yr	Not given	Mid thigh amputa- tion and x-ray as prescribed	Death from pulmo- nary metastases 4 yr. later
Idem	25	Male	Left poplit- eal space	None	Positive	Positive	3 mo.	Bursal cyst	Local excision	Recurrence in 4 mo., and death from pul- monary metastases 5 mo later
Idem	27	Male	Left poplit- eal space	None	None	Positive	5 wk.	Not given	Excision and x-ray as prescribed	Under treatment for second recurrence
Lazarus and Marks, 1913	30	Male	Palm of hand	9	None	Positive	3 yr.	Synovial sarcoma	Local excision and x-ray as prescribed	Well 14 mo. later
Idem	17	Female	Knee	None	Positive	Positive	15 mo.	Bursitis	Local excision and x-ray as prescribed	Diffuse metastases to abdomen and lymph nodes 1½ mo later

## METASTATIC BRAIN ABSCESS

### COMPLICATING INCONSPICUOUS PULMONARY SUPPURATION IN THE PRESENCE OF CHRONIC NONTUBERCULOUS EMPYEMA

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DURING the years 1934 to 1941, inclusive, 343 cases of nontuberculous empyema have been treated in the University of Michigan Hospital. Of these, 132 were considered chronic. All cases classified as chronic had a known duration of three months or longer. Six of these cases of chronic empyema were complicated by metastatic brain abscesses, an incidence of 4.5 per cent. The diagnosis in each case was confirmed by post-mortem examination. The review of these cases was stimulated by the recent, unexpected death of two patients having chronic empyema, occurring within a three-day period. The cause of death in both patients was a metastatic brain abscess.

This study was begun solely as a review of the cases of chronic nontuberculous empyemas complicated by metastatic cerebral abscesses. A careful study of the post-mortem findings in each revealed that five of the six cases reported harbored a variety of pulmonary lesions beneath the empyema space, each of which was a probable source of septic emboli. In only one case was the pulmonary tissue underlying the pleural space free of suppuration. The significance of these findings became evident when it was found that in four cases no residual empyema space existed at the time of death.

Such metastatic cerebral abscesses follow the occlusion of cerebral vessels by an infected embolus, arising at the site of intrathoracic suppuration and circulating freely in the blood stream (Eagleton). The course of the embolus, from its point of origin to its terminal lodging, has occasioned various theories. Virchow, in 1853, postulated an origin in a small tributary of one of the pulmonary veins, the particle being then transported through the pulmonary veins, the left heart, and the carotid artery and deposited in a terminal radical of a cerebral artery. Eagleton,<sup>3</sup> however, believes that the pathway of the emboli from the chest to the brain is entirely venous and asserts that the rapidity of arterial flow tends to prevent lodgment of an embolus in the arterial circulation. His premise that the emboli pass entirely through veins gains some confirmation in the work of Batson<sup>4</sup> who has demonstrated connections between the intercostal and azygos veins, the paravertebral venous plexus and the cerebral veins. Because of the low pressure within this system and the absence of valves, reversal of flow readily occurs with increase in

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ages, each presumably inadequate. There was relief of symptoms after each drainage for a short period of time.

The patient had been in ill health for six weeks prior to admission. Five days before admission he became irrational and in the interim before admission there had been two generalized convulsions. The temperature was 97° F.; the patient was obviously moribund. There was questionable rigidity of the neck. The left thorax showed retraction and limited expansion with the physical signs of a considerable pleural effusion. The blood pressure was 130/61. A small draining sinus was noted in the left mid-axilla; above it, two healed scars were visible. The liver was enlarged. All reflexes were hyperactive and ankle clonus was sustained bilaterally. The patient died eight hours after admission. Roentgenograms were not obtained.

Post-mortem examination revealed a right frontal lobe abscess measuring 1 by 4 cm. It was not walled off from the surrounding brain tissue. The abscess cavity contained heavy green pus under considerable pressure. There was a fibrinopurulent pachymeningitis in the region of the abscess. The chest showed a chronic undrained left empyema, the surrounding pleural wall of which was from 2 to 4 mm. in thickness. The empyema space contained bloodstained purulent material. The draining sinus in the seventh intercostal space entered a small cavity containing necrotic lung, but it did not communicate with the empyema. The underlying pulmonary tissue showed acute passive congestion and edema with a chronic pneumonitis near the hilum.

CASE 3.—R. S. (No. 41883) was a white man, aged 51 years. The patient was admitted to the University Hospital on December 15, 1937. He had been apparently well until October, 1936, when he developed a right "pleural pneumonia," with which he was in bed for three weeks. Following this he was somewhat improved, but continued to have mild symptoms until May, 1937. At this time a right-sided empyema was diagnosed and drained. A drainage tube was left in place for a period of seven months and was removed shortly before admission. The sinus track drained intermittently after removal of the tube. He had recently complained of pain in the right chest, and had developed a cough productive of yellow sputum. Six days before admission there was a sudden onset of generalized tonic convulsions, mostly of the right side, which lasted for one half hour. There was no loss of consciousness or incontinence. Two more attacks occurred during the evening of the same day and lasted from ten to fifteen minutes each. For the next four days the patient appeared normal. On the day before his admission, there was again loss of consciousness without muscle twitching or incontinence. Following recovery, the patient was drowsy and appeared to have a poor memory. His speech was thick and difficult to understand. On December 15, the day of admission, there were three more attacks, each lasting about thirty minutes, and without vomiting, headache, or incontinence. The temperature was 99.6° F. Examination revealed a complete aphasia and a slight right facial palsy. A complete flaccid paralysis of the right arm and leg was present. There were no signs of increased intracranial pressure. Roentgenograms showed an unresolved pneumonia with a small localized empyema. After admission there was increasing lethargy and a daily temperature elevation to 100° F. Craniotomy was deferred in the hope that the suspected brain abscess would become walled off. Terminally the temperature rose to 103° F. and the patient had marked dyspnea. He died on the fifth hospital day.

At post mortem examination a brain abscess, measuring 3 by 2.5 cm., occupied the left precentral area. The abscess had ruptured into the left lateral ventricle which contained thick, greenish-gray, foul pus. The path of extension showed very little reaction. In addition, a fibrinopurulent pachymeningitis and leptomeningitis were noted about the left cerebrum and the undersurface of the brain. The right pleural space was almost completely obliterated by dense adhesions below the third rib anteriorly and posteriorly. The pleurae measured 1 cm. in thickness. No free pus

intrathoracic pressure, as in coughing or straining. At least two possible routes are thus open for an infected embolus freed from its empyema source to gain entrance into a cerebral vessel.

### CASE REPORTS

CASE 1.—J. G. (No. 368464) was a white man, aged 43 years. The patient was admitted to the University of Michigan Hospital on Sept. 6, 1935, complaining of a productive cough and pain in the right lower chest. The previous history related the onset of acute mid-abdominal pain in 1928, following drainage of a right subdiaphragmatic abscess, in another hospital. A series of bronchoscopic aspirations, before admission to the University Hospital, had given no relief of his presenting pulmonary symptoms.

On admission the scar at the site of the previous subdiaphragmatic drainage appeared well healed. The temperature was 99.5° F. The patient was not acutely ill. Roentgenograms revealed a chronic pneumonitis at the right base with an obliterative pleuritis. After lipiodol bronchograms had been made, a small saccular area, thought to be a small pleural abscess, was noted at the extreme anterior axillary segment of the middle lobe. Thoracentesis revealed pus containing *Streptococcus viridans*. A rib resection was done on September 15, and an empyema cavity was entered. There was a communication with a small subdiaphragmatic abscess, and a fistulous track entered a branch of the middle lobe bronchus. The postoperative course was essentially uneventful. Because of a small, persistently draining sinus, a segment of osteomyelitic rib was removed on October 24. At the time of the patient's discharge from the hospital on November 27, there was a draining sinus at the empyema drainage site which, upon probing, led inward for three inches toward the resected rib. The bronchopleural fistula had closed.

On Jan. 12, 1936, the patient was readmitted because of persistent drainage, apparently due to further osteomyelitic involvement of the sixth rib. Roentgenograms showed an osteomyelitis and an extensive pleuritis at the right base. Further resection of the involved rib was done on January 15, at which time the bronchopleural fistula was again demonstrated. Again the patient's course was uneventful until, on February 13, there was a sudden loss of consciousness with difficult respiration. The attack lasted about one hour. The blood pressure during this period was 90/60. There were no convulsions and no localizing signs during the attack. During the following two days the patient complained of a frontal headache and there was some drowsiness. On February 19, the drowsiness became more marked and the patient became disoriented. At no time were convulsions noted. Neurologic examination revealed slight fullness of the retinal veins without papilledema. The reflexes, both deep and superficial, were normal. Because of the absence of definite localizing signs, craniotomy was not done. The patient died on February 21.

Post-mortem examination revealed a frontal lobe abscess measuring 7 cm. in diameter. Grossly, the adjacent white matter was yellowish green in color and very hyperemic. Microscopically, the brain tissue forming the wall of the abscess was extensively destroyed and was undergoing liquefaction necrosis. There was an associated leptomeningitis at the base of the brain, and particularly in the cisterna magna. The pleural space on the right was obliterated by dense adhesions except at the site of the bronchopleurocutaneous fistula. The underlying pulmonary tissue disclosed a chronic fibroid pneumonia with a chronic purulent bronchitis and bronchiectasis.

CASE 2.—G. W. (No. 402288) was a white man, aged 33 years. The patient was admitted to the University Hospital in coma on May 14, 1937. A scanty history, obtained from his relatives, revealed that an empyema had been drained six years

and the patient was unconscious. There was no definite evidence of any other abnormality for a short period of time.

The patient had been in bed for six weeks prior to admission. For days before admission he became restless and in the afternoon before admission there had been two periods of convulsion. The temperature was 101° F. The patient was obviously moribund. There was considerable rigidity of the neck. The left thoracic cavity contained the lung and contained very little fluid. The right thoracic cavity contained the lung and contained very little fluid. A small amount of fluid was noted in the left pleural cavity. The lungs were pale and the heart was normal. The patient died on the day after admission. Blood examinations were not obtained.

Post-mortem examination revealed a large frontal lobe abscess measuring 4 by 4 cm. It was not filled of fluid and surrounded by a capsule. The abscess cavity contained heavy cream pus under an adherent membrane. There was a fibrinopurulent exudate in the space of the abscess. The chest showed a chronic undulant left empyema in the surrounding pleural cavity of which was from 2 to 4 cm. in fluid depth. The empyema fluid contained flocculent purulent material. The lungs were normal in the lower lobes but showed a small cavity containing necrotic lung but it did not communicate with the empyema. The underlying pulmonary tissue showed some pus but no abscess and a small cavity pneumothorax near the hilum.

Case 2.—A 35-year-old male was admitted to hospital on 15th June. The patient was admitted to the University Hospital on 15th June 1957. He had been apparently well until 10th June when he developed a right pleural pneumonia and when he was in bed for two weeks. Following this he was somewhat improved but continued to have mild symptoms until 10th July 1957. At this time a right-sided empyema was diagnosed and drained. A drainage tube was left in place for a period of seven months and was removed during the previous admission. The tube tract healed uneventfully after removal of the tube. He had recently complained of pain in the right chest and had developed a cough productive of yellow sputum. Six days before admission there was a sudden onset of generalized tonic convulsions, mostly of the right side which lasted for one-half hour. There was no loss of consciousness or incontinence. Two more attacks occurred during the evening of the same day and lasted from ten to fifteen minutes each. For the next four days the patient appeared normal. On the day before his admission there was a total loss of consciousness without muscle twitching or incontinence. Following recovery the patient was febrile and appeared to have a poor memory. His speech was thick and difficult to understand. On December 12, the day of admission there were three more attacks each lasting about thirty minutes and without vomiting, headache or incontinence. The temperature was 101° F. Examination revealed a complete right arm and a right leg focal palsy. A complete focal palsy of the right arm and leg was present. There was no change of increased intracranial pressure. Blood examinations showed an increased pneumonia with a small localized empyema. After admission there was increasing lethargy and a daily temperature elevation to 101° F. Craniotomy was deferred in the hope that the supposed brain abscess would become visible. Fortunately the temperature rose to 101° F. and the patient had marked dysmetria. He died on the fifth hospital day.

A post-mortem examination of a brain abscess measuring 1 by 2.5 cm. occupied the left posterior horn. The abscess had ruptured into the left lateral ventricle which contained thick cream-colored fluid pus. The path of extension showed very little reaction. In addition, a fibrinopurulent pachymeningitis and leptomeningitis were noted about the left hemisphere and the undersurface of the brain. The right pleural space was almost completely obliterated by dense adhesions below the third rib anteriorly and posteriorly. The pus was measured 2 cm. in thickness. No free pus



intrathoracic pressure, as in coughing or straining. At least two possible routes are thus open for an infected embolus freed from its empyema source to gain entrance into a cerebral vessel.

### CASE REPORTS

CASE 1—J. G. (No. 368464) was a white man, aged 43 years. The patient was admitted to the University of Michigan Hospital on Sept. 6, 1935, complaining of a productive cough and pain in the right lower chest. The previous history related the onset of acute mid abdominal pain in 1928, following drainage of a right subdiaphragmatic abscess, in another hospital. A series of bronchoscopic aspirations, before admission to the University Hospital, had given no relief of his presenting pulmonary symptoms.

On admission the scar at the site of the previous subdiaphragmatic drainage appeared well healed. The temperature was 99.5° F. The patient was not acutely ill. Roentgenograms revealed a chronic pneumonitis at the right base with an obliterative pleuritis. After lipiodol bronchograms had been made, a small saccular area, thought to be a small pleural abscess, was noted at the extreme anterior axillary segment of the middle lobe. Thoracentesis revealed pus containing *Streptococcus viridans*. A rib resection was done on September 15, and an empyema cavity was entered. There was a communication with a small subdiaphragmatic abscess, and a fistulous track entered a branch of the middle lobe bronchus. The postoperative course was essentially uneventful. Because of a small, persistently draining sinus, a segment of osteomyelitic rib was removed on October 24. At the time of the patient's discharge from the hospital on November 27, there was a draining sinus at the empyema drainage site which, upon probing, led inward for three inches toward the resected rib. The bronchopleural fistula had closed.

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Post mortem examination revealed a frontal lobe abscess measuring 7 cm. in diameter. Grossly, the adjacent white matter was yellowish green in color and very hyperemic. Microscopically, the brain tissue forming the wall of the abscess was extensively destroyed and was undergoing liquefaction necrosis. There was an associated leptomeningitis at the base of the brain, and particularly in the cisterna magna. The pleural space on the right was obliterated by dense adhesions except at the site of the bronchopleurocutaneous fistula. The underlying pulmonary tissue disclosed a chronic fibroid pneumonia with a chronic purulent bronchitis and bronchiectasis.

CASE 2—G. W. (No. 402288) was a white man, aged 33 years. The patient was admitted to the University Hospital in coma on May 14, 1937. A scanty history, obtained from his relatives, revealed that an empyema had been drained six years previously. The wound had healed but had required three or four subsequent drain-

sions had been present for a week prior to admission. Examination after admission revealed a right hemiplegia with some sensory changes. The small residual empyema was well drained. A craniotomy was performed by Dr. Carl F. List on the day following admission and an unencapsulated brain abscess in the left parasagittal area was drained. *Str. viridans* was cultured from the evacuated pus. The patient received 6 Gm. of sulfathiazole daily from the time of admission. The post-operative course was steadily downhill with increasing coma. Death occurred on May 23.

At post-mortem examination a multiloculated, unencapsulated brain abscess was present in the left parietal area. There were four locules, each measuring at least 2 cm. in diameter and all communicating with each other. There was a diffuse purulent leptomenigitis. No evidence of skull fracture was found. The left pleural space was obliterated by an adhesive pleuritis except for a small sinus track at the site of previous drainage; no free pus was present. The underlying pulmonary tissue showed extensive fibroid pneumonia, bronchiectasis, and a terminal, purulent, lobular pneumonia. Several small hemorrhagic infarcts were noted.

CASE 6.—E. O. (No. 481806), a white man, aged 31 years, was admitted to the University Hospital on May 22, 1941, with a two day history of staggering gait and repeated left sided convulsions. In February, 1941, he had had an attack of pneumonia complicated by a right empyema. Following drainage on three occasions he improved, but was still in poor general health, although not confined to bed. On admission, a small draining sinus was noted in the lower right posterior chest. There were physical signs of pleural fluid over the lower half of the right chest posteriorly. The patient was semi-stuporous and had weakness of the left side of the body. The sinus track in the right side of the chest was dilated and a larger tube was inserted, releasing several ounces of thick pus. By probing, the empyema cavity was found to extend to the thoracic dome. Neuro-surgical consultation on admission suggested the diagnosis of metastatic brain abscess. Craniotomy by Dr. Ward W. Woods, May 26, revealed an abscess in the right parietal lobe and the abscess was drained through an exploring needle. *Str. viridans* was cultured from the pus. The patient received 6 Gm. of sulfanilamide daily from May 24, until his death on May 27.

Post-mortem examination revealed an unencapsulated right parietal lobe abscess measuring 3 by 1 cm. There was a diffuse purulent leptomenigitis over the right cerebrum. The empyema was dependently and adequately drained. The lung beneath the empyema showed a chronic fibroid pneumonia, bronchiectasis, and an acute purulent and hemorrhagic pneumonia, probably terminal. A thrombus containing many leucocytes was noted in a small pulmonary vein.

#### DISCUSSION

It has been stated by Evans<sup>1</sup> that it is the tendency of chronic empyemas to form a chronic type of brain abscess, which is generally solitary and almost invariably the only lesion indicative of pyemia. In none of our reported cases, however, was chronicity of the brain abscess a noteworthy factor. Four of our cases showed a duration of from five to ten days from the onset of symptoms to death. The patient with a brain abscess in Case 5 was operated upon eight days after onset; he died thirteen days after operation. In four of the cases the abscess was solitary; in one, multilocular, and in one, multiple.

The cause of death in most reported cases<sup>8</sup> was due to rapid extension of the abscess, with frequent rupture of the abscess into a ventricle. In our third and fourth cases, rupture occurred into the lateral ventricles.

was present. The subjacent lung showed a chronic fibroid pneumonia with organizing fibrin in the alveoli. There were multiple microscopic pulmonary abscesses throughout. The liver contained a chronic abscess cavity measuring 3 cm. in diameter.

CASE 4.—B. F. (No. 420322) was a white boy, aged 4 years. The patient was admitted to the University Hospital on March 26, 1938. In August, 1937, he was seen by his physician because of a stiff neck, pain over the left trapezius muscle, and fever. These symptoms disappeared spontaneously. During the first part of March, 1938, they reappeared, and in addition, a hot, tender swelling appeared over the trapezius.

On admission, the temperature was 99.4° F. There was a 10 cm., indurated, tender, poorly outlined mass over the left trapezius muscle. A left scoliosis was present. Dullness to percussion with diminished breath sounds and fremitus was noted at the left pulmonary apex posteriorly. Roentgenograms of the chest showed obscuration of the left apex, diminished aeration of the left lung, and increased soft tissue shadows in the left cervical and supraclavicular areas with included gas in the tissues. A diagnosis of empyema necessitatis was made, and thoracentesis posteriorly yielded thick, foul, yellow pus which contained *Str. viridans*, fusiform bacilli, and Spirochaetae. Drainage of the empyema through the fourth rib bed posteriorly was carried out on April 4, 1938. At operation the empyema cavity extended from the fourth rib to the apex of the thoracic dome. The postoperative course was uneventful until April 7, when the patient suddenly became unresponsive. No convulsions were noted. Examination at this time revealed left facial weakness, slight weakness of the left arm and leg, papilledema, a positive Kernig's sign, and bilateral sustained ankle clonus with a positive Babinski sign. Lumbar puncture showed increased pressure and a clear fluid which contained thirty cells per cubic millimeter, lymphocytes predominating. The clinical impression was a right cerebral abscess, probably metastatic. A craniotomy was performed on the same day by Dr. Carl F. List, disclosing a nonencapsulated right frontal lobe abscess from which a *Str. viridans* was cultured. After sealing the meninges to the cortex with an electrocautery, the abscess was opened and packed. Sulfonamide therapy was started on the day of operation and was continued until death twenty-three days later.

Post-mortem examination revealed a huge, drained brain abscess replacing the entire right frontal lobe, with extensive surrounding suppurative encephalitis. The purulent process had ruptured into the right lateral ventricle, from which there had been extension into the opposite lateral ventricle and the fourth ventricle. There was a small undrained abscess in the left parietal lobe. A diffuse purulent leptomeningitis was present. Examination of the thorax showed an obliteration of the pleural space over the left apex with a 5 cm. draining sinus posteriorly. No free pus was present. The underlying lung showed an acute purulent bronchitis and a few scattered areas of bronchial pneumonia in the right and left lower lobes.

CASE 5.—H. K. (No. 475011), a white man, aged 35 years, was admitted to the University Hospital on Feb. 3, 1941. He had been referred to the hospital with mild fever, chronic debility, and inadequate drainage of a postpneumonic empyema of three months' duration. Roentgenograms on admission revealed an extensive pyopneumothorax extending from the diaphragm to the thoracic dome on the left side. There was a narrow sinus posteriorly which drained a small amount of thick pus. The sinus track was dilated and a drainage tube of adequate size inserted. Constant negative pressure was maintained in the empyema space by means of a suction apparatus. Re-expansion of the lung almost completely obliterated the empyema space in eight weeks' time. The patient was discharged in good condition with a small tube in the chest wall. He was readmitted on May 9, 1941, with a story of good health until two and one-half weeks previously, when a fall while intoxicated resulted in a contusion of the left supra-orbital area. There was no loss of consciousness at the time. Vertigo, mild nausea, and recurrent right-sided convul-

sions had been present for a week prior to admission. Examination after admission revealed a right hemiplegia with some sensory changes. The small residual empyema was well drained. A craniotomy was performed by Dr. Carl F. List on the day following admission and an unencapsulated brain abscess in the left parasagittal area was drained. *Str. viridans* was cultured from the evacuated pus. The patient received 6 Gm. of sulfathiazole daily from the time of admission. The post-operative course was steadily downhill with increasing coma. Death occurred on May 23.

At post-mortem examination a multiloculated, unencapsulated brain abscess was present in the left parietal area. There were four locules, each measuring at least 2 cm. in diameter and all communicating with each other. There was a diffuse purulent leptomeningitis. No evidence of skull fracture was found. The left pleural space was obliterated by an adhesive pleuritis except for a small sinus track at the site of previous drainage; no free pus was present. The underlying pulmonary tissue showed extensive fibroid pneumonia, bronchiectasis, and a terminal, purulent, lobular pneumonia. Several small hemorrhagic infarcts were noted.

CASE 6.—E. O. (No. 481806), a white man, aged 31 years, was admitted to the University Hospital on May 22, 1941, with a two-day history of staggering gait and repeated left-sided convulsions. In February, 1941, he had had an attack of pneumonia complicated by a right empyema. Following drainage on three occasions he improved, but was still in poor general health, although not confined to bed. On admission, a small draining sinus was noted in the lower right posterior chest. There were physical signs of pleural fluid over the lower half of the right chest posteriorly. The patient was semi-stuporous and had weakness of the left side of the body. The sinus track in the right side of the chest was dilated and a larger tube was inserted, releasing several ounces of thick pus. By probing, the empyema cavity was found to extend to the thoracic dome. Neuro-surgical consultation on admission suggested the diagnosis of metastatic brain abscess. Craniotomy by Dr. Ward W. Woods, May 26, revealed an abscess in the right parietal lobe and the abscess was drained through an exploring needle. *Str. viridans* was cultured from the pus. The patient received 6 Gm. of sulfanilamide daily from May 24, until his death on May 27.

Post-mortem examination revealed an unencapsulated right parietal lobe abscess measuring 3 by 1 cm. There was a diffuse purulent leptomeningitis over the right cerebrum. The empyema was dependently and adequately drained. The lung beneath the empyema showed a chronic fibroid pneumonia, bronchiectasis, and an acute purulent and hemorrhagic pneumonia, probably terminal. A thrombus containing many leucocytes was noted in a small pulmonary vein.

#### DISCUSSION

It has been stated by Evans<sup>1</sup> that it is the tendency of chronic empyemas to form a chronic type of brain abscess, which is generally solitary and almost invariably the only lesion indicative of pyemia. In none of our reported cases, however, was chronicity of the brain abscess a noteworthy factor. Four of our cases showed a duration of from five to ten days from the onset of symptoms to death. The patient with a brain abscess in Case 5 was operated upon eight days after onset; he died thirteen days after operation. In four of the cases the abscess was solitary; in one, multilocular, and in one, multiple.

The cause of death in most reported cases<sup>8</sup> was due to rapid extension of the abscess, with frequent rupture of the abscess into a ventricle. In our third and fourth cases, rupture occurred into the lateral ventricles.

In all the cases, a purulent meningitis was present. In none was true encapsulation present. Kahn<sup>9</sup> is of the opinion that metastatic abscesses, with the exception of those associated with a generalized pyemia, are caused by mixed organisms and do not tend to become encapsulated. In the cases reported in this series, anaerobic cultures of the evacuated pus were not obtained. Grant<sup>2</sup> states that the thorough walling off of a subcortical area of infection within the brain requires about four weeks from the onset of symptoms. In our six cases the duration of symptoms from onset to death ranged from five to twenty-three days.

The ante-mortem diagnosis in each of our cases was a metastatic brain abscess whose site of origin was a chronic empyema. At post-mortem examination, however, the empyema cavity was found completely obliterated in four of the six cases; the pleurae were fused into a thick, heavily scarred layer and only a sinus track in the thoracic wall remained. These findings suggest that pleural infection was quite unlikely as the source of the brain abscess, at least in these four patients. Autopsy did show that bronchiectasis was present in four of the six patients (Case 6 had, in addition, a thrombus in one of the small pulmonary veins) and that multiple, small microscopic pulmonary abscesses were present in the fifth case (Case 3). Only in Case 4 was chronic intrapulmonary suppuration absent; empyema was, therefore, the most likely source of the emboli to the brain only in this patient.

Hedblom<sup>10</sup> reports 310 cases of chronic empyema with one death from a metastatic brain abscess. This is the only published report of the incidence of this complication in a given number of cases of chronic empyema. The status of the lung beneath the empyema pocket was not described.

The reported incidence of empyema in metastatic brain abscess has shown considerable variation in the reports of brain abscess associated with some form of intrathoracic suppuration. In none of the reported figures are the empyemas classified as either acute or chronic and no account is given of the pulmonary tissue adjacent to the empyema space. Schorstein,<sup>7</sup> in 1909, reported 19 cases of metastatic brain abscess from intrathoracic suppuration, of which three are said to have resulted from empyema, an incidence of 15.7 per cent. In 1931, Evans<sup>1</sup> reported 22 cases of brain abscess, five or 22.7 per cent occurring in the presence of empyema. In 1934, Cohen<sup>5</sup> reported 19 cases, four of which also had empyema, an incidence of 21.0 per cent, while Nickerson,<sup>6</sup> in 1935, found only one empyema in 12 cases of brain abscess, an incidence of only 8.3 per cent. The metastatic abscesses not reported as due to empyema were assumed to have arisen from either pulmonary abscess or bronchiectasis which was clinically present in the nonempyema cases. King,<sup>8</sup> in reviewing the reported cases of metastatic brain abscess from empyema or pulmonary suppuration in 1936, found only two patients living following operation for brain abscess that had occurred in the presence of empyema. He assumed that the abscesses were well encapsulated in both cases.

In the above 72 collected cases with metastatic cerebral abscesses quoted from various authors, 82 per cent arose from intrinsic pulmonary suppuration and only 18 per cent, or 13 cases, were attributed to empyema. We are of the opinion that a high percentage of these 13 cases would have shown some degree of suppuration in the adjacent pulmonary tissue if this had been closely examined, and that if such pulmonary suppuration were present it was a more likely source of metastatic brain abscess than the empyema.

#### SUMMARY

1. During the years 1934 to 1941, inclusive, 343 cases of empyema have been admitted to the University of Michigan Hospital. Of this group, 132 cases were considered chronic. Six of these patients with chronic empyema died of metastatic cerebral abscess, an incidence of 4.5 per cent.

2. The six cases with their autopsy findings are reported in detail. In four of the cases the previous empyema space was obliterated. Five of the six cases displayed varying degrees of chronic parenchymal pulmonary suppuration. This was considered a more probable source of emboli than the pleural infection.

3. Adequate and dependent drainage of the empyema was established in four of the six cases after admission to the hospital. No definite correlation was noted between manipulation at the empyema drainage site and the onset of cerebral symptoms.

4. In four of the reported cases the cerebral abscess was solitary; in one, multiple, and in one, multilocular. In none of the cases has encapsulation of the abscess been present. All had a purulent meningitis and in two cases rupture of the abscess into the adjacent lateral ventricle occurred.

5. In three cases of brain abscess exploratory craniotomy was done; in two of the cases the abscess was drained surgically, while in one the abscess was evacuated through the exploring needle. Appropriate chemotherapy with one of the sulfonamide compounds was carried out in these three cases.

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NaCl solution. The thromboplastin suspension was incubated for ten minutes at 50 to 55° C. with intermittent stirring. The supernatant fluid was decanted after standing ten minutes at room temperature and was mixed with an equal volume of CaCl<sub>2</sub> solution.

3,3'-Methylene-bis-(4-hydroxycoumarin)\* in 0.1 and 0.2 per cent concentrations was suspended in 2 per cent acacia. This suspension was administered orally with a syringe and a blunt 18 gauge needle. The mice received from 10 to 100 mg. per kg. daily for three days and the tests were performed on the fourth day. After the tests were completed the animals were sacrificed and examined grossly for evidence of subcutaneous hemorrhage.

### RESULTS

The normal bleeding time varied from 27 to 222 seconds in this group of mice, which was in agreement with previous findings.<sup>4</sup> Coagulation time with the capillary method ranged from 60 to 255 seconds with an average of 153.4 seconds. Prothrombin time in 62 duplicate tests was 15 to 28 seconds with an average of 22.4 seconds. When the bleeding time and the coagulation time were longer than 300 seconds, the values were considered significantly prolonged. Prothrombin time longer than 30 seconds was considered abnormal.

Results on 10 mice which received 4.8 to 6.0 mg. of 3,3'-methylene-bis-(4-hydroxycoumarin) orally per 20 Gm. of mouse weight within a period of 72 hours are tabulated in Table I. The results show normal variation

TABLE I

BLEEDING, COAGULATION, AND PROTHROMBIN TIME IN MICE BEFORE AND AFTER THE ORAL ADMINISTRATION OF 3,3'-METHYLENE-BIS-(4-HYDROXYCOUMARIN) FOR THREE DAYS

MOUSE NUMBER	BLEEDING TIME (SEC- ONDS)	COAGULA- TION TIME (SEC- ONDS)	PRO- THROM- BIN TIME (SEC- ONDS)	TOTAL DOSE PER 20 GM. (WEIGHT IN MG.)	BLEEDING TIME (SEC- ONDS)	COAGULA- TION TIME (SEC- ONDS)	PRO- THROM- BIN TIME (SEC- ONDS)
11	124	185	26	4.8	120 420	165	28
43	66	130	18	4.8	34 480	158	24
44	75	165	20	4.8	45 300	495	169
2	42	60	21	4.8	190 118	870	109
1	87	85	23	4.8	55 120	1050	148
6	96	195	25	6.0	780	301	47
31	138	180	24	6.0	136 360	1200	>180
35	67	168	24	6.0	>900	1500	>180
26	122	122	21	6.0	105 115	65	26
37	190	178	21	6.0	180 120	93	22

\*Supplied kindly by Dr. J. F. Biehn, Abbott Laboratories, North Chicago, Ill.



# BLEEDING TIME IN MICE FOLLOWING THE ORAL ADMINISTRATION OF 3,3'-METHYLENE-BIS- (4-HYDROXYCOUMARIN)

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LINK and his associates<sup>1</sup> showed that the hemorrhagic agent in spoiled sweetclover hay prolonged the prothrombin time in animals. Butt and co-workers<sup>2</sup> and Bingham and co-workers,<sup>3</sup> following the administration of the hemorrhagic agent to human beings and dogs, observed prolongation of coagulation and prothrombin times. We found that excessive doses of heparin injected subcutaneously into mice prolonged the coagulation time and in some cases the bleeding time.<sup>4</sup> Therefore, it was of interest to determine if the hemorrhagic agent identified by Stahmann, Huebner, and Link,<sup>5</sup> when administered orally to mice, would affect the bleeding time. The coagulation and prothrombin times were compared with the bleeding time to evaluate better the degree of bleeding tendency produced by this substance.

## METHODS

Bleeding times were determined as previously described.<sup>4</sup> Coagulation times were done by the capillary method on blood from the tip of the mouse's tail.

Prothrombin times were performed on oxalated blood drawn from the mouse's heart. No difficulty was encountered with this test. Values will check closely if the following procedure is adhered to for the amount of sodium oxalate used. A 1 c.c. syringe with a 25 gauge needle was rinsed in distilled water. Sodium oxalate was drawn to the 0.2 c.c. mark and then the syringe was emptied. The volume of sodium oxalate which remained in the needle was found to be 0.05 c.c. With this volume of sodium oxalate, 0.2 c.c. of blood was diluted and mixed in the syringe. Prothrombin time studies were done in duplicate tests on 0.1 c.c. of blood placed on dry glass spot plates. A mixture of 0.2 c.c. of equal parts of rabbit brain thromboplastin suspension and  $\text{CaCl}_2$  solution was added. The prothrombin time was determined by probing the contents on the spot plate with a pointed glass rod. The salt solutions and the thromboplastin used in this study were prepared as described by Quick.<sup>6</sup> Rabbit brain thromboplastin, 100 mg., was suspended in 5 c.c. of 0.9 per cent

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prothrombin time in these groups was in excess of three minutes. Two mice bled 300 and 360 seconds; they also had prolonged coagulation and prothrombin times (Groups 11 and 17). Three mice bled from 480 to 870 seconds (Group 5); one mouse which was tested had a normal coagulation time; the other two died soon after the bleeding time test, from blood loss. Two mice had prolonged bleeding time with normal coagulation and prothrombin times (Group 10). Two mice had prolonged bleeding time with normal coagulation time and slightly prolonged prothrombin time (Group 16). Eleven mice had normal bleeding time and markedly increased coagulation and prothrombin times (Groups 6, 12, 14, and 18). Only one mouse exhibited a prolonged prothrombin time, while the other tests were normal (Group 7). At autopsy 14 of the 41 mice which were examined had hematomas. Some animals had from one to several hematomas, varying in size from a few millimeters to one centimeter in diameter, usually just beneath the skin. They were found on the feet, legs, back, abdomen, neck, and ears. Out of 25 mice with prolonged bleeding or prothrombin times, 12 mice had hematomas. In the remaining 16 mice with normal prothrombin, coagulation, and bleeding times, two mice had hematomas.

#### DISCUSSION

The hemorrhagic agent, when given in adequate doses, will prolong the bleeding time in mice. The mechanism by which 3,3'-methylene-bis-(4-hydroxycoumarin) prolongs bleeding in mice is not understood at present. It is certain that heparin prolongs the coagulation of blood in a different way than the hemorrhagic agent, due to the immediate anticoagulant action of heparin *in vivo* and *in vitro*, and because it does not affect the prothrombin time. The hemorrhagic agent, on the other hand, increases both the coagulation and the prothrombin time *in vivo*. Link and associates<sup>7</sup> suggested, from dilution studies on normal and pathic rabbit plasmas, that the action of 3,3'-methylene-bis-(4-hydroxycoumarin) was not necessarily restricted to the prothrombin time mechanism. Even though we did not do dilution studies on mouse's heart blood, we believe that when our values were in excess of 30 seconds they were significantly prolonged.

It is difficult to offer an explanation for the lack of correlation between the bleeding time and the coagulation and prothrombin times in some of the animals. In those instances where the bleeding time was normal with prolonged coagulation and prothrombin times, long bleeding times might have followed one or more normal bleeding time values. We did not subject the animals to more than two bleeding time tests, since excessive blood loss could have affected the coagulation and prothrombin times, which were done after the bleeding time tests. Link and associates<sup>7</sup> observed whole plasma prothrombin times of approximately 10 minutes in dogs, and in excess of 250 seconds (12.5 per cent plasma) in rabbits and rats without any tendency to hemorrhage, following large doses of

in bleeding time, coagulation time, and prothrombin time, and the effect of the hemorrhagic agent on these tests. Mice 11 and 43 showed prolonged bleeding time with normal coagulation time and prothrombin time. Usually, we found when one of the tests was normal, the remaining two were also in the normal range as indicated by Mice 26 and 37. However, mice were found in which the prothrombin time and the coagulation time were prolonged while bleeding time was normal (Mice 1 and 2). Most frequently, however, when the bleeding time was prolonged, the coagulation time and the prothrombin time were also increased (Mice 6, 31, 35, and 44). Table I shows that a marked disparity can occur between duplicate bleeding time tests. In some animals a prolonged bleeding time was present with the first pricking (Mice 6 and 35); in other instances, however, it was necessary to prick the mouse a second time to induce long bleeding (Mice 11, 31, 43, and 44).

TABLE II

COMPARATIVE STUDIES OF DIFFERENT TESTS ON MICE WHICH RECEIVED 3,3'-METHYLENE-BIS-(4-HYDROXYCOUMARIN) ORALLY FOR THREE DAYS

GROUP	NUMBER OF MICE	MG./KG. DAILY	RANGE OF BLEEDING TIME (SECONDS)	RANGE OF COAGULATION TIME (SECONDS)	RANGE OF PROTHROMBIN TIME (SECONDS)	HEMATOMA	
						POSITIVE	NEGATIVE
1	7	10	25-152	45- 139			
2	7	20	29-127	70- 230			
3	6	40	52-184	44- 312			
4	1	60	> 900	417	D		1
5	3	60	480-870	211*	D	2	1
6	2	60	195-285	480- 870	127->180	1	1
7	1	60	64	58	42		1
8	8	60	60-232	85- 215	18- 24		8
9	1	80	> 900	D	D	1	
10	2	80	420-480	158- 165	24- 28	1	1
11	1	80	300	495	169		1
12	4	80	63-154	600-1590	149->180	2	2
13	4	80	60-180	125- 256	23- 32		4
14	4	80	38-110	362- 458	56-142		2
15	4	100	> 900	480-1500	> 180*	3	1
16	2	100	420-660	174- 301	30- 47		2
17	1	100	360	1200	> 180	1	
18	1	100	113	1860	140	1	
19	3	100	110-210	65- 180	22- 26	2	1

\*Done on one mouse because the remaining mice in the group died.

D, Died.

Longest bleeding time value was taken if there was a disparity between duplicate tests.

Table II summarizes the effect of various doses of the hemorrhagic agent on the bleeding time, coagulation time, prothrombin time, and hematoma formation in 62 mice. Thirty-five mice which were treated with 10 to 100 mg. per kg. did not exhibit any changes in either the bleeding, coagulation, or the prothrombin times (Groups 1, 2, 3, 8, 13, and 19). Prolonged values in one or more tests occurred in the remaining 27 mice. Out of 43 mice which received from 60 to 100 mg. per kg., 15 mice had bleeding times longer than 300 seconds. Six mice given this treatment had bleeding times in excess of 900 seconds (Groups 4, 9, and 15). The

days bleeding was frequently initiated. These findings on clot resistance indicate that the hemorrhagic agent may prolong bleeding and impair both the firmness of the clot and its ability to adhere to the skin wound.

Hematomas were the only clinical manifestation effected by the hemorrhagic agent. In Group 8 negative tests corresponded with the absence of hematomas, although this was not the case in two animals in Group 19; we found hematomas even when the bleeding time, coagulation and prothrombin times were normal. They were not, on the other hand, always present when one or more tests exhibited abnormal values. It must be borne in mind that the origin of hematoma formation was not known. It may be assumed that the occurrence of a hematoma could be due to trauma in those animals which acquired a hemorrhagic tendency after treatment with 3,3'-methylene-bis-(4-hydroxycoumarin).

#### SUMMARY

1. A prothrombin time test was developed in mice, using 0.1 c.c. heart blood. Prothrombin time values ranged from 15 to 28 seconds and averaged 22.4 seconds.

2. Following oral administration of 60 to 100 mg. per kg. of 3,3'-methylene-bis-(4-hydroxycoumarin) over a period of three days, the bleeding time was prolonged in some of the mice.

3. Comparison of bleeding time with coagulation and prothrombin times showed a lack of correlation in many of the mice. Some animals had prolonged bleeding times with normal coagulation and prothrombin times, while others had prolonged coagulation and prothrombin times with a normal bleeding time.

4. Hematomas were more frequently found in mice with prolonged bleeding time or prothrombin time than in mice with normal values.

5. The relation of bleeding time and prothrombin time to hemorrhagic tendency was discussed. It appeared that still other factors which were discussed are involved in hemostasis.

We are indebted to Dr. Karl Paul Link who kindly sent to one of us (A. L. C.) his unpublished paper, which was helpful in the interpretation of our results.

#### REFERENCES

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3,3'-methylene-bis-(4-hydroxycoumarin). These findings demonstrate that the prothrombin time may not necessarily indicate a bleeding tendency. The phenomenon of prothrombin time is not well understood at present. One of us (A. L. C.) advanced the view that inactive thrombin, which is present in the circulating blood, plus a complementary factor constitute the prothrombin complex.<sup>5</sup> Prothrombin is only a precursor of thrombin in that in the heparin-prothrombin complex, preformed thrombin is inactivated by antithrombin which is composed of heparin and the complementary factor. Thromboplastin in the presence of calcium and the complementary factor has its neutralizing effect upon heparin, thus activating the thrombin. On this basis it was assumed that the prothrombin time expresses the speed with which the activation of thrombin occurs and the degree of concentration of the activated thrombin from the prothrombin complex. The prothrombin time, therefore, does not necessarily measure the prothrombin content.

It is quite possible that still another factor, probably present in the skin,<sup>4</sup> functions in the mechanism of hemostasis. Even though the skin (or tissue) factor is a hypothetical substance, we believe it may well play a role in either prolonged or normal bleeding in mice which receive the hemorrhagic agent. It may be that excessive amounts of the skin factor are present in mice with normal bleeding time and prolonged coagulation and prothrombin times. Likewise, decreased amounts of the skin factor may be present in mice with long bleeding time and normal coagulation and prothrombin times. Experiments in heparinized mice suggest that variable amounts of the skin factor are present.<sup>4</sup>

We found no petechiae in our mice during life or at autopsy; neither were we able to find any reference in the literature<sup>2, 3</sup> regarding petechiae in human beings after treatment with the hemorrhagic agent. We doubt that the hemorrhagic agent exerts a loosening effect on the cement substance of the capillary endothelial cells. Bingham, Meyer, and Pohle<sup>3</sup> reported that arteriolar, capillary, and venule dilatation occurred in dogs which received the hemorrhagic agent. It may well be that prolonged bleeding may follow dilatation of the smaller vessels; however, we feel that a more likely explanation for the prolonged bleeding is due to changes in the characteristics of the clot. We believe heparin and the hemorrhagic agent may delay the hemostasis which more adequately is measured by the clot resistance test<sup>8-11</sup> *in vivo* and the clot firmness test *in vitro*.<sup>12</sup>

The following method of clot resistance was used to determine the ability of the clot to resist increases in venous pressure in mice.<sup>11</sup> The venous bleeding time was determined after transversely cutting a vein in the middle portion of the mouse's tail with a stylet measuring 0.5 by 1.5 mm. In an attempt to renew bleeding, a cuff pressure of 75 mm. of Hg was applied proximal to the wound from 18 to 34 minutes after bleeding had stopped. Out of 109 normal mice this pressure provoked bleeding in 5.5 per cent, whereas in mice treated with the hemorrhagic agent for three

days bleeding was frequently initiated. These findings on clot resistance indicate that the hemorrhagic agent may prolong bleeding and impair both the firmness of the clot and its ability to adhere to the skin wound.

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# A NEW METHOD OF SKIN PROTECTION FOR ILEOSTOMIES AND COLOSTOMIES

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ONE of the most annoying complications following an ileostomy or colostomy is the irritation caused by the constant contact of the surrounding skin with the discharging fecal material. It is during the immediate postoperative period, before a suitable bag can be fitted because of edema of the stoma, that this complication is most likely to occur. The resultant maceration of the skin may become so extensive as to cause the patient more pain and discomfort than the original disease.

We have attempted to prevent this condition by utilizing the various ointments (zinc oxide, vaseline, aluminum paste, etc.) recommended in standard texts but have not had much success. The diarrhea that occurs even with the use of a proper diet and constipating medication washes away the ointment in a short time and exposes the skin to the irritating action of the stool. Even with a more solid stool, the admixture of the ointment and fecal material directly on the skin makes the changing of dressings a slovenly procedure for the nurse and an unpleasant one for the patient.

Following the suggestion of DeBakey and associates,<sup>1</sup> we tried using a solution of vinylite resin\* for this purpose but found that this also could not withstand the continual washing effect of the fecal material. However, on mixing collodion with the vinylite resin an excellent, thick, impermeable transparent film is obtained which is easy to apply and adheres closely to the skin. Since we have been using this solution, the absence of skin irritation in all types of enterostomies has been striking and a source of gratification to both patient and surgeon.

The formula used is as follows:

Vinylite resin	25 Gm.
Acetone	100 c.c.
Collodion	25 c.c.

## DIRECTIONS FOR USE

1. The first application of the solution is best done immediately prior to opening the enterostomy.
2. Any ointment which is present is completely removed and all of the skin area completely cleansed with ether and acetone.

\*This material was supplied through the courtesy of the Carbon and Carbide Chemicals Corporation, Chicago, Ill.

Received for publication, June 1, 1942.

3. The solution is poured on the skin around the incision and smeared evenly with an applicator or tongue depressor. The sides of the exteriorized bowel may be covered with the solution without any harmful effect.

4. At least ten to twenty minutes must be allowed for thorough drying of the solution and the formation of an adequate film.

5. The bowel is then opened and a dry sterile dressing applied.

6. The solution is reapplied without removing the previous coats as often as necessary depending upon the consistency and amount of the fecal drainage. This may vary from several times daily to once every few days.

The solution may also be used to advantage for protection of the skin in cases of fecal fistulas and profusely draining infected wounds.

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# Recent Advances in Surgery

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CONDUCTED BY ALFRED BLALOCK, M.D.

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## PRINCIPLES IN THE PROTECTION OF PATIENTS WHO RECEIVE BLOOD

PAUL HOXWORTH, CINCINNATI, OHIO

*(From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital)*

**D**URING the past ten years there has been a marked increase in the number of blood transfusions in almost all hospitals, since indications for their use have become more generally and clearly understood. This is particularly true in surgery. The value of blood therapy in controlling fluid balance, in nutrition, in the treatment of traumatic and thermal shock, in hemorrhage, in infection, and in wound healing is much better known and is becoming still more widely recognized.

Most surgeons show little interest in and lack knowledge of the careful laboratory work necessary before blood can be given safely in transfusion. The laboratory is too often considered a remote agency entrusted with a trivial routine responsibility, that of grouping and matching blood prior to transfusion. Moreover, the surgeon is inclined to give uncritical acceptance to those methods in use in the hospital. Yet in the smaller hospitals the responsibility for selection of blood usually falls to a house doctor, who was exposed to the theories and technique of grouping and matching for one morning during the sophomore year of his medical school training, and in the larger hospitals to a technician burdened with too many duties to give special thought to one problem.

Details of preoperative preparation, operative procedure and technique, and postoperative management, including nursing care, are subjected to critical supervision by the attending surgeon. Yet all these efforts to apply the best known standards of safety may be and frequently are neutralized, either by delay as a result of uncertainty in the laboratory or by an error which precipitates a hemolytic transfusion accident. Just seven years ago at the Cincinnati General Hospital a young woman came to thoracoplasty after sanatorium management had proved to be inadequate. She received careful preoperative preparation, good anesthesia, and excellent surgery. She died during her first postoperative day shortly after receiving 300 c.c. of incompatible blood in transfusion. Recheck of the grouping and direct match tests showed agglutination of the donor cells at the end of one hour by both the anti-A test serum and the recipient's serum. This was not detectable at the end of one-half hour. The methods and materials which had been provided and

which had proved adequate for the usual blood specimen had been accepted uncritically by the surgical house officer responsible for the laboratory work.

Since that time I have been intimately connected with the laboratory aspect of blood transfusion. As volunteer director of the Red Cross Blood Transfusion Service which was developed in the department of surgery of the University of Cincinnati and which serves the entire Cincinnati area, I have had an opportunity to encounter many problems at the Cincinnati General Hospital and fourteen other hospitals, concerning the grouping and matching of blood. It becomes of importance to relate some of the pitfalls which have come to my attention so frequently that I cannot help but believe that proper standards of safety are frequently ignored.

The purpose of this article is to draw the attention of clinicians to the causes of frequent accidents and delays which for the most part could be avoided.

As a result of our experience with a carefully supervised series of more than 12,000 blood transfusions given during four years we have concluded that the vast majority of transfusion accidents and delays are due to a lack of knowledge and application of the following principles.

1. *The Use of Test Serums of High Titer.*—The titer of a and b agglutinins and A and B agglutinogens in the blood of individuals is known to vary widely. Despite this, it is common practice in many hospitals to select group A and group B individuals as donors for test serums merely because the agglutinating effect of their serums on one or two specimens of anticells appears to be quite pronounced. Test serums selected in this manner may fail or offer poorly defined criteria of agglutination when placed with A or B cells with less pronounced agglutino-gen activity. Borderline criteria of agglutination may result in errors in grouping or delay in providing blood due to uncertainty in the laboratory. During the past year two cases have come to our attention in which donors of subgroup  $A_2$  were grouped as O for this reason. In each case the group A blood was given to a group O recipient, resulting in death of the recipient.

Unfortunately, reliance cannot always be placed upon the agglutinin titer of commercially prepared test serums. All test serums to be used, whether prepared in the hospital or in the commercial laboratory, should be selected because of superlative agglutinin titer. Determinations may be made by the use of the Coca<sup>1</sup> method of slide titration or by the method of serial titration.<sup>2</sup> Definitions of safe titers have been made repeatedly<sup>3</sup> but very few laboratory technicians know the titer of the test serums which are in current use in their own laboratories.

2. *Failure to Observe a Well-Known Principle of Agglutination.*—It is a very common practice to select a group O donor for a group AB recipient if a member of the latter blood group is not available. The

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If the blood is needed urgently, this confusion becomes hazardous. Increased time and expense affect the laboratory.

We have observed many such situations and they arise most frequently in the following circumstances: 1. Occasional effect of sulfonamide blood concentration; 2. sepsis with high sedimentation rates; 3. severe hemorrhage and other extreme anemias; 4. leucemia; 5. cold agglutinations due to the use of icebox samples in the test.

False agglutination due to these conditions can be promptly distinguished from true agglutination in practically all cases by the use of the following laboratory principles. First, by performing the direct match test with an open technique on a slide and stirring to break up the clumps under the microscope. In true agglutination agitation by stirring produces more marked agglutination. If specimens on a slide are placed under moist Petri dishes, this technique is possible. Sealed cover slip preparations for compatibility tests make it impossible. Second, microscopic examination of the patient's blood diluted in saline solution will in the above situation show the same false agglutination effect.

*5. Performance of Compatibility Tests Before All Transfusions, Even Though the Blood Is of the Same Group.*—Recently a case came to our attention in which a recipient of blood group  $A_2B$  was given two transfusions of group B blood because AB blood was not available. Twenty-four hours later a succeeding compatibility test with group AB blood showed incompatibility. This was presumably due to an accumulation of anti-A antibodies of sufficient potency to agglutinate the A cells in the blood which was being tested.

In some hospitals compatibility tests are not performed, reliance being placed wholly upon the grouping and the transfusion of like groups. The known existence of rare atypical agglutinins and the possibility of the ever present human factor of error in determining blood groups make it necessary that compatibility tests be performed in order to safeguard the patient receiving blood.

*6. The Use of Rh- Donors.*—Recently unquestionable evidence that hemolytic transfusion reactions occasionally may be caused by incompatible Rh factors has been produced.<sup>4</sup> Routine tests to distinguish Rh+ from Rh- red cells are impracticable at present because of the extreme difficulty in providing anti-Rh serums in amounts that would be required. It is possible for the hospital laboratory to secure a small amount of anti-Rh serum and to maintain a list of Rh- donors. It is also possible to perform modified direct match tests for anti-Rh factors.<sup>5</sup> These should be reserved for use (1) for patients who are or who have been recently pregnant, (2) for patients who are receiving multiple transfusions over periods of days, and (3) for the newborn with erythroblastosis fetalis.

principle of dilution is relied upon to inactivate incompatible a and b agglutinins in the donor's serum. In the past year one case has come to our attention in which this factor resulted in death because the a agglutinin in the serum of the donor was of unusually high titer. Similar cases are reported in the literature. If group A donors are selected for group AB individuals, only one incompatible antigen-antibody complex is present and its potency may be determined easily by the use of a simple quantitative direct match test.

3. *Close Observation of the Patient During Transfusion.*—With the advent of blood banks and the increased requirement, blood transfusion has become very commonplace and informal. In many instances the transfusion is begun and a busy intern feels it necessary to leave in order to accomplish other work. Unfortunately, mistakes in grouping and matching of blood and confusion of specimens in the laboratory do occur. This is particularly true where blood banks are in operation, despite careful regulation, and may result in transfusion of incompatible blood. Early symptoms may not appear in a hemolytic transfusion reaction, but they frequently do, and the interruption of the transfusion by the attending physician may be lifesaving. Two cases which occurred at the Cincinnati General Hospital are in striking contrast and serve to illustrate the importance of close early observation.

No. 1.—A group A blood was given to a patient belonging to group O. Seventy-five cubic centimeters were given when the patient complained of paresthesia in the extremities and precordial pain and the transfusion was interrupted. Later oliguria, hemoglobinuria and uremia and laboratory recheck established the diagnosis of a hemolytic transfusion reaction. The patient recovered.

No. 2.—A group A blood was given to a patient belonging to group B, due to confusion of specimens. The transfusion was begun and the patient was not observed by a physician throughout. He received 500 c.c. of incompatible blood. Anuria and death due to uremia followed.

Although there are many factors contributing to the severity of a reaction other than the amount of incompatible blood which a patient receives, it is reasonable to believe that interruption of a blood transfusion after only a few cubic centimeters of incompatible blood have been given affords more chance for recovery. If early mild subjective complaints or objective signs are to be regarded as contraindications for continuing transfusion, it is difficult to condone any practice wherein a physician is not observing the patient carefully.

4. *Delays in the Laboratory Due to False Agglutination Being Interpreted as True Agglutination.*—Almost every week a case comes to our attention in which donor after donor of the same blood group as the patient is rejected by a laboratory because false agglutination is interpreted as true agglutination in the direct match test. The causative factors of this phenomenon are almost always attached to the blood of the patient and numerous samples of compatible blood are rejected.

## Book Reviews

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**Ophthalmology and Otolaryngology.** A manual prepared and edited by the Subcommittee on Ophthalmology and Otolaryngology of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Harry S. Gradle, Chairman of Ophthalmology; Harris P. Mosher, Chairman for Otolaryngology. Volume II, Military Surgical Manuals. Pp. 331, with 126 illustrations. Philadelphia and London, 1942, W. B. Saunders Company. Cloth. \$4.00.

This is the second volume in the series of six volumes comprising twelve military surgical manuals which are being developed under the auspices of the Division of Medical Sciences of the National Research Council. These manuals are to furnish the Medical Departments of the United States Army and Navy with a digest of necessary information in the field of military surgery. Most of the manuals deal with highly specialized surgical subjects. The digest of present-day information is to help the Army or Navy surgeon to apply skill when the necessity arises, to a field which may not be his own.

This volume gives approximately equal space to ophthalmology and to otolaryngology. The eight chapters on ophthalmology are contributed by five well-known oculists. The subject matter deals with functional testing, examination of the eye, acute visual disturbances, acute inflammations, injuries, medical treatment, local anesthesia about the orbit, and surgical procedures.

The section on otolaryngology is divided into seventeen chapters contributed by twelve otolaryngologists of note. A variety of subjects are discussed: primary treatment of gunshot wounds of the face, the ear in general, fractures of the temporal bone and of the cribriform plate, injuries to the labyrinth and labyrinthine function, group testing of hearing, malingering, roentgenologic diagnosis of petrositis, the ear in military aviation, re-education of the deafened soldier, re-education for speech defects, the nose and throat in general, paralysis in connection with wounds in the throat, infections of the throat, chemotherapy, injuries of the esophagus, and injuries of the larynx, hyoid bone, and trachea.

This small manual seems to fulfill the purpose for which it is intended, a brief digest of up-to-date information on the ophthalmologic and otolaryngologic problems of the military surgeon, not the specialist in these fields, but the nonspecialist.

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**War Medicine.** A Symposium edited by W. S. Pugh, Commander, U. S. N., for the Philosophical Library. Pp. 565, illustrations, 76. New York, 1942, F. Huhner and Company, Inc.

This volume represents a symposium of articles dealing with medical military subjects, as selected from the current medical journals of America and Britain. Under the editorship of W. S. Pugh, Commander, U. S. N., retired, fifty-seven articles have been chosen for inclusion in the book, and have been arranged in three sections, namely, Surgery, Aviation and Naval Medicine, and General Medicine. The subjects or articles selected represent a splendid variety of subjects which would be of vital interest to medical officers on duty.

Naturally, in a symposium of this type there can be no correlation of material such as would be achieved by one author. Moreover, since the material is presumably not edited from the standpoint of scientific statements, numerous errors

## SUMMARY AND CONCLUSIONS

The difficulties in blood transfusion outlined above are more common than is generally supposed and most of them can be corrected by better observance of the known standards of safety. This requires (1) the use of test serums of highest titer, (2) a more popular knowledge and application of the established principles of hemagglutination, and (3), close observation of the patient during transfusion as added insurance against laboratory error.

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Naturally, in a symposium of this type there can be no correlation of material such as would be achieved by one author. Moreover, since the material is presumably not edited from the standpoint of scientific statements, numerous errors



or contradicting statements are encountered. Although the article dealing with burns, beginning with page 41, correctly emphasizes the necessity of débridement, on page 21 in a paragraph dealing with burns, is a statement, "no attempt at surgical cleaning is made"; this latter statement is erroneous, and is contradictory to those in the article on burns beginning on page 41. On page 22, the maximum limit of 40 Gm. sulfanilamide for a patient would appear to be needlessly high. The reviewer was surprised to see at the bottom of page 144, the statement that a four-tail bandage "will also give some temporary support to a fracture of the mandible"; in his experience such a dressing exerts too much backward displacement, thereby tending to obstruct the pharyngeal airway.

The authors quote too freely from experiences in World War I. The chapter on burns, however, is one of many exceptions to this criticism; it thoroughly discusses the tannic acid and triple dye methods along with other procedures as practiced in Britain during this war. Unfortunately, this material and the book were apparently assembled a few weeks or months too early to allow inclusion of the pressure dressing method of Koch and Reid.

Although the section on Surgery is not up to the standard of the other two sections, the articles on "Gunshot Wounds of the Heart," "Blast Concussion," "Blood Substitutes" and "Drainage of the Pleura" are splendid contributions. The article on "War Wounds and Compound Fractures" contains a splendid historical review of Lister's principles of asepsis, and the proper emphasis on the importance of immobilization in the treatment of wounds as well as fractures.

Considering how meager is our knowledge of aviation medicine, the section dealing with this subject is remarkably informative and well written. With the information contained in these articles alone a flight surgeon could obtain a good insight into the proper care of pilots, and treatment of symptoms derived from the hazards of centrifugal force and changes in altitude.

Altogether the book is very informative and interesting. Although it cannot be used as a text because it is deficient in various subjects, it nevertheless would be of inestimable value as an addition to a medical military library.

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**Anatomy of the Hand; The Principles of Anatomy as Seen in the Hand.** By Frederic Wood Jones, D.Sc., F.R.S., F.R.C.S., University of Manchester, England. Ed. 2. Pp. 407, with 144 illustrations. Baltimore, 1942, Williams & Wilkins Company. \$7.50.

This book was prepared during the 1914 War as a guide for a series of lectures in applied anatomy as a part of the course of instruction to officers of the R. A. M. C. The first edition was published in 1920.

Written by the professor of anatomy at the University of Manchester, the material is authoritatively presented. The second edition has been revised, and six new chapters and twenty new figures have been added. The author's interesting style and practical descriptions should make the subject matter attractive to professional groups in the related medical sciences.

The first fourteen chapters contain an interest for comparative anatomists, while the surgical interest is attracted to the succeeding ten concise chapters, devoted to the practical anatomy of the fascias, bones, joints, muscles, tendons, and tendon sheaths of the hand. The remaining nine chapters are devoted to discussions on the functions of the hand, the motor and sensory pathways, the nerves, the vascular channels, and lymphatics.

This book will be of interest to the student of anatomy, and especially the busy medical officer of the R. A. M. C., for whom it is primarily intended.

**Sulfanilamide and Related Compounds in General Practice.** By Wesley W. Spink, M.D., F.A.C.P. Pp. 374, with charts and table. Chicago, 1942, Year Book Publishers, Inc. \$3.

This book has been greatly increased in size and comprehensiveness. In a field which is advancing and changing as fast as any in medicine, and in which the amount of published material is almost overwhelming, this little book constitutes an admirable condensation of the present knowledge of the subject and will serve as an up to date and authentic guide and summary for the surgeon as well as for the medical man. Few are the professional men today who can afford to do without this excellent monograph.

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**The Principles of Neurological Surgery.** By Loyal Davis, M.S., M.D., Ph.D. Ed. 2. Pp. 503, with 298 illustrations. Philadelphia, 1942, Lea & Febiger. \$7.

This is a much improved second edition of a neurosurgery text, the first edition of which was published in 1936.

Some of the material has been rewritten and rearranged. The chapters are much better subdivided by subchapter headings; for example, Chapter IV, Intracranial Abscess, which had no subdivisions in the first edition, is now subdivided into Etiology and Pathogenesis, Pathology, Symptoms, and Surgical Treatment. Some new sections are added, such as electroencephalography, arachnoiditis, tuberculosis of the skull, herniation of intervertebral disc, and others. The illustrations have been rearranged, many new ones added, and some of those in the first edition deleted. All of these improvements and additions have increased the book size from 416 pages to 494 pages.

This is the only available textbook of neurosurgery and, therefore, is the only place where all of this material is collected together. It is recommended to the general practitioner and others who occasionally need some information concerning the more common neurosurgical problems.

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**Urological Diseases of Pregnancy.** By L. G. Crabtree (with a chapter by G. C. Prather). Pp. 472, with 158 illustrations. Boston, 1942, Little, Brown & Company.

The problems relating to the urinary tract in pregnancy have been pretty well covered, a little at a time, by a great number of authors in widely scattered books and periodicals, but this work is the first to come to the attention of the reviewer, in which the pertinent data are assembled, together with a very extensive bibliography. Its value is, of course, enhanced by the extensive personal experience of the author at the Boston Lying In Hospital and in private practice.

There are fairly extensive discussions of the effects of pregnancy upon the body and upon its economy in general, as well as upon the urinary tract itself. There are chapters comparing the effects of pregnancy in lower animals with those in the human being as well as with the effects of tumors other than the pregnant uterus upon the urinary tract. The work is of particular practical value to the urologist and general practitioner because of its discussions of special problems which, while they may be commonplace to the busy obstetrician, are puzzling to the physician who encounters them only occasionally. I refer to the situations created by pyelonephritis, atony of the bladder, tuberculosis of the urinary tract, stones, solitary kidneys, renal neoplasms, and the like. The techniques of examination and modes of treatment are well covered, as is the relationship of the toxemia of pregnancy to the urinary tract.

Of interest to nearly all practitioners are the chapters on the oliguria of transfusion reactions, and the untoward effects of the sulfonamides on the urinary tract.

The critical reviewer can, of course, find points which arouse him, although they are minor ones, as the very frequent use of "scarification" to mean cicatrization or, more simply, scarring and of "physiology" for function, as well as "etiology" for cause. The last two are, of course, attributable to the widespread, if deplorable, use of medical slang.

One regrets that the discussions of the cause of hydronephrosis in pregnancy, and of the effect of tumors of the female pelvis upon the kidneys are treated so briefly, and one shudders at the author's failure to discuss the value of nasal suction (Wangensteen and Paine) in ileus, the more so because the author mentions the high mortality of the condition.

The book is warmly recommended to urologists, obstetricians, and general practitioners, and should be a valuable source of references for investigators in the fields concerned.

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**First Aid, Surgical and Medical: An Advanced Guide.** By Warren H. Cole, M.D., F.A.C.S., and Charles B. Puestow, M.D., Ph.D., F.A.C.S., University of Illinois, Ed. 1. Pp. 351, illustrations 92. New York, 1942, D. Appleton-Century Company, Inc.

At a time when the war has caused large numbers of civilians to be trained in the essentials of first aid, an authoritative and yet elementary textbook is of first importance. This readable book fulfills this need admirably.

An excellent introduction precedes the descriptions of procedures for specific injuries, and although it is verbose in places, it nevertheless offers an excellent background of knowledge for the first-aid worker. There are sections on each of the types of conditions to be encountered in either civil or military life, such as shock, lacerated wounds, fractures, burns, gas and bomb injuries, etc.

There are some points in the book with which most physicians would take issue, such as several of the types of bandages described, yet the vast bulk of the material is accurate, correct, and well expressed. This book is not for beginners, as the title indicates, but those who have had a rudimentary first-aid course will find it of inestimable value in achieving a further understanding of the subject.

The title implies that this book contains material only for the use of the lay first-aid worker, but the majority of general practitioners would find it of great value in medical practice.

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# SURGERY

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## Original Communications

### ACUTE CRANIOCEREBRAL TRAUMA

#### SURGICAL AND PATHOLOGIC CONSIDERATIONS BASED UPON 151 CONSECUTIVE AUTOPSIES

E. S. GURDJIAN,\* M.D., J. E. WEBSTER, M.D., AND H. ARNKOFF,† M.D.  
DETROIT, MICH.

THE material herein presented comprises the results of observations made upon post-mortem examinations of 151 patients who died following cranial trauma. The examinations were performed at the Wayne County Morgue, Detroit, Mich. They represented a consecutive, unselected group admitted to the morgue throughout a period of eight months, from July, 1939, to March, 1940. The hospital records of those patients who were hospitalized before death were also studied for pertinent correlations.

This analysis is not intended for statistical purposes, but it is an attempt to correlate the pathologic features and the surgical management of cases of head injury. A survey of the pathologic background should serve to amplify surgical and medical concepts of treatment.

*Material.*—Gross evidence of brain damage was found in every case, although in a few instances the pathologic changes were minimal (Fig. 1). Combinations of lesions were of frequent occurrence. For purposes of clarity, the pathologic findings were classified into main groups on the basis of the outstanding type of lesion present (Table I).

*Age Distribution.*—The well-recognized observation that the mortality rises with the higher age groups among patients with head injury is shown in Table II. Even though the incidence of major head injury is less in childhood, the evidence shows that children tolerate the effects of trauma much better than do patients in higher age groups.

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†Medical Corps, U. S. Army.

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TABLE I

Fracture of the skull		112
Compound fractures		29
Gunshot etiology		18
No fractures		39
Epidural hemorrhages (surgical)		11
Associated with fracture	10	
Unassociated with fracture	1	
Epidural hemorrhages (small)		4
Acute subdural hematoma (surgical)		22
Acute subdural hematoma (small)		12
Chronic subdural hematoma		1
Massive intracerebral clot		1
Petechial hemorrhages	54	
With gunshot wounds	17	71
Contusions of the brain surface with softening		72
Cerebral fat embolism		2

TABLE II  
AGE DISTRIBUTION

AGE GROUPS (YR)	NUMBER OF CASES
Under 5	8
5 to 10	1
10 to 20	11
20 to 30	27
30 to 40	24
40 to 50	28
Over 50	52

TABLE III

CHART SHOWING RELATIONSHIP OF ETIOLOGY TO PATHOLOGY FOUND IN AUTOPSY SERIES

ETIOLOGY	NUMBER OF CASES	PATHOLOGY						
		FPI DURAL HEM.	SUB DURAL HEM.	SUB ARACH NOID HEM.	MAS SIVE INTRA CEREBRAL BRAIN HEM.	PTTF CHIAI HFM.	FRAC TURE	CON TUSION
Fall	23	3	8*	5	0	11	15	12
Direct trauma	1	0	0	0	0	1	1	1
Auto accident	90	4	12	28	1	29	66	72
Electricity	2	0	0	1	0	2	0	0
Fights	6	1	2	0	0	3	1	5
Bullet wounds	18	—	—	—	—	17	18	—
Explosion	1	0	0	0	0	1	1	0
Train accidents	3	0	1	1	0	2	2	1
Auto Bicycle accidents	5	3	0	1	0	1	1	1
Unknown cause of death	2	0	0	1	0	1	1	0
Total	151	11	27*	37	1	71	112	72

\*One case of chronic subdural hematoma

*Etiology.*—Direct blow to a fixed or nonfixed head is common. The head is usually injured by indirect blows; that is, the head in motion strikes a nonmoving or slower moving object. In either of the latter groups, multiple lesions occur as well as injuries to other parts of the



Fig. 1.—An example of minimal cerebral damage involving the frontal lobe. This patient, aged 35 years, was struck by an auto. There was no fracture of the skull. He survived injury for 7 days (associated injury, fractured tibia).

body (Fig. 2). Of interest in the tabulation of the causes of injury is the frequent association of epidural hemorrhage and bicycle accidents. In Table III the etiologic factors and the resultant pathologic changes have been correlated.

*Time of Death.*—In 133 cases, the time of death was classified and is shown in Table IV. Of note is the fact that sixty-one victims were dead

TABLE IV  
TIME OF DEATH

TIME OF DEATH	NUMBER OF CASES
Dead on admission	61
1 hr.	2
2 hr.	5
3 hr.	12
5 hr.	5
10 hr.	5
15 hr.	2
20 hr.	5
30 hr.	7
2 days	6
3 days	5
4 days	3
5 days	1
Over 5 days	14

upon admission, while thirty-six died within twenty hours after entrance to the hospital, a group which represents 72.1 per cent of the total.

*Fractured Skull.*—Fracture of the skull was present in 112 instances. In twenty-nine the fracture was compounded; eighteen of the latter were caused by gunshot wounds. Head injury unassociated with fracture of



Fig. 2.—An example of profound cranial damage with comminution of the middle fossa and destruction of the left optic nerve. The fracture line extends from the left orbit and frontal region to the pituitary fossa and across the length of the petrous bone of the left side.

the skull occurred in thirty-nine patients. Of the instances in which a fracture was found to be present, the site of the fracture was localized to the anterior third of the skull in 22.9 per cent of the cases; to the middle third in 45.3 per cent, and to the posterior third in 32.7 per cent (Table V).

TABLE V  
LOCALIZATION OF FRACTURE

LOCALIZATION	NUMBER OF CASES
Anterior 3rd	6
Middle 3rd	35
Posterior 3rd	18
Anterior and middle	11
Middle and posterior	11
Anterior, middle, and posterior	17

TABLE VI  
CHART OF SITE OF CONTUSIONS

SITE	NUMBER OF CASES
Inferior frontal	R—24 L—25
Inferior temporal	R—23 L—22
Frontal (lateral and superior)	R—10 L—9
Temporal (lateral and superior)	R—27 L—20
Parieto-occipital	R—10 L—12
Cerebellum and brain stem	R—5 L—4

The distribution of the fracture lines is more graphically represented in Fig. 3.

*Cerebral Contusions.*—An outstanding finding in the examination was the occurrence of contused areas of the cortex of the hemispheres (Fig. 4). There were 191 instances of such areas among seventy-two of the cases. For the sites of the contusions, see Table VI.

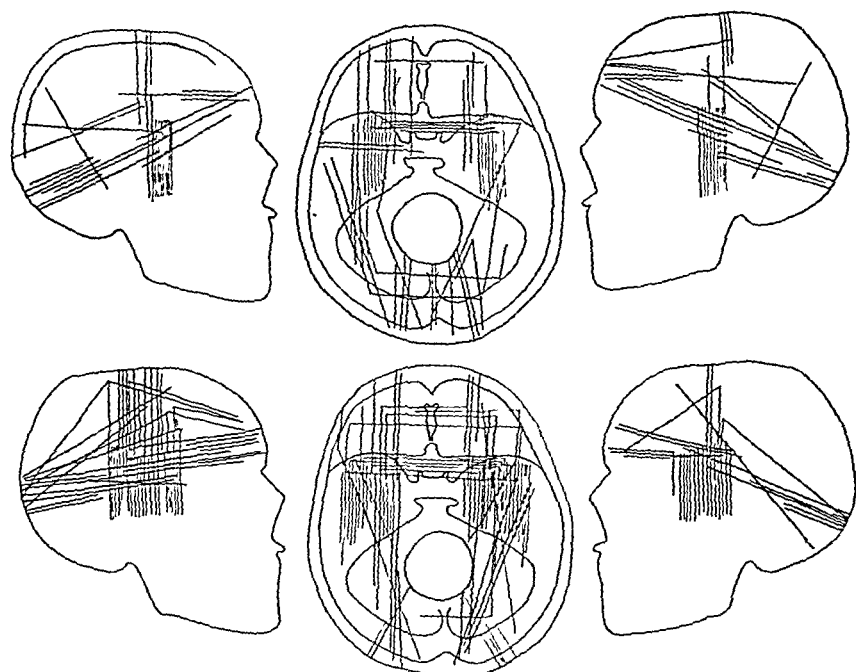


Fig. 3.—Diagrammatic representation of fractures in ninety-four cases. Right lateral, basal, and left lateral views are shown in two rows. The most common site of fracture is the middle third of the skull (45.3 per cent).



Fig. 5 demonstrates the aggregations of the areas involved by bruising of the brain. They are shown in upper and lower groups, to make the diagram more intelligible.

#### ACUTE SUBDURAL HEMORRHAGE

In this series, subdural hematoma of surgical proportions (about 30 Gm. and over) was found in twenty-two cases, and in twelve additional cases small hemorrhages in the subdural space were discovered. The latter includes cases of very minimal hemorrhages in the subdural space up to the amount of about 30 Gm. in size. The larger subdural hematomas were unilateral in each instance. In the group with insignificant subdural hemorrhage, there were four bilateral cases.



Fig. 1.—An example of multiple cerebral contusions located in commonly involved areas. This patient, aged 52 years, was involved in an automobile accident; he had a lucid interval and then progressive stupor. Bilateral trephines were made on the tenth day with evacuation of bilateral subdural hydriomas. He expired the eleventh day.

The subdural hemorrhage occurred in the fronto-parieto-temporal region in the greatest majority of cases (Fig. 6). In one there was a collection of blood in the region of the optic chiasm. In another, a fronto-parietal hematoma extended between the hemispheres and over the corpus callosum. There was one case of hematoma over the left cerebellar hemisphere. The fronto-parieto-temporal localization of the subdural lesion was evident in thirty of thirty-four cases (including both surgical and small subdural hemorrhages). A frontoparietal trephine opening two inches on either side of the midline would have uncovered the clot in each of the thirty cases.

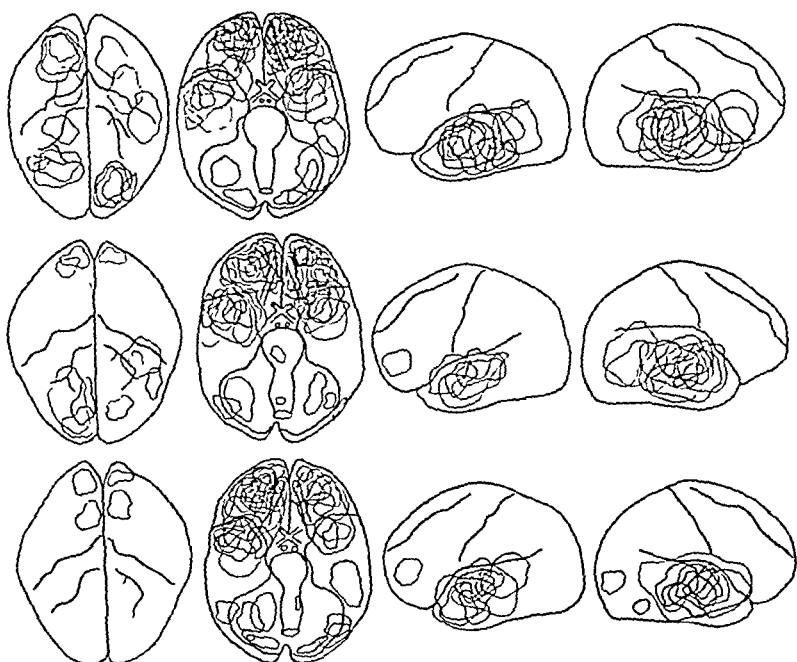


Fig. 5.—Diagrammatic representation of 191 contusions in seventy-two cases. The superior, basal, right, and left lateral views of the brain are shown with the overlying contusions (represented by outline) in three rows. Contusions occurred most frequently on the inferior surfaces of the frontal and temporal lobes.

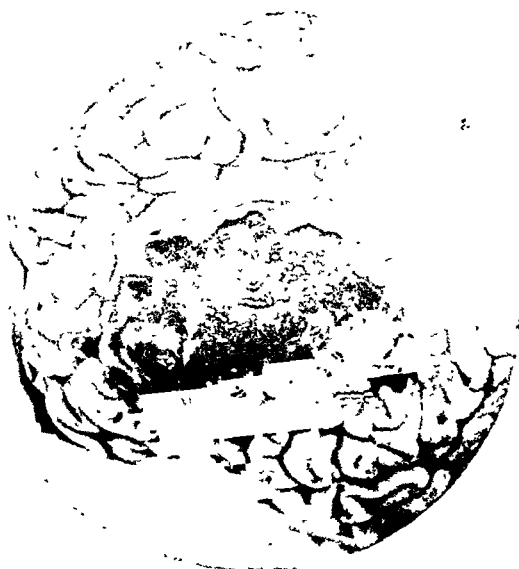


Fig. 6.—An example of one of the acute subdural hematomas encountered. This patient, aged 44 years, was hospitalized after an auto accident. He was unconscious; B. P. 130/90; expired 5 hours later.

The bleeding arose from torn pial vessels on the convexity of the hemispheres. In three cases, an intracerebral clot extended into the subdural space through the tear in the brain. Contusions of the brain surface on the same and on the opposite sides were seen in thirteen cases. Only infrequently were they thought to be the source of the subdural hemorrhage. Subarachnoid hemorrhage was seen in three patients. Petechial hemorrhages were noticed in seven instances, with hemorrhages in the pons and the medulla in four. Epidural bleeding was accompanied by minor subdural hemorrhages in four cases.

Purely on the basis of post-mortem findings, six of the twenty-two might have recovered following operative intervention. The remaining sixteen had profound associated injuries in other parts of the nervous system. Among those with small clots in the subdural space, the associated lesions elsewhere in the brain were marked, and they were thought to be the cause of death.

The position of the clot could not have been guessed on the basis of a fracture line. In eight cases the fracture was on the opposite side from the subdural lesion. There was no fracture in seven cases. The more pertinent facts about these cases of subdural hemorrhage are classified in Table VII.

TABLE VII

SURGICAL (TWENTY-TWO CASES—30 GM. AND OVER) AND NONSURGICAL SUBDURAL HEMORRHAGES (ELEVEN CASES)

	SURGICAL	NONSURGICAL
Side involved		
Right	15	4
Left	7	3
Bilateral	0	4
Fracture		
Same side	7	
Opposite side	8	
Present	15	11
None	7	0
Position of cranium		
Fronto-parieto-temporal	20	10
Basal about chiasm and pons	1	1
Interhemispheric	1	0
Over cerebellar lobe	1	1
Associated pathology		
Contusions and tears	13	Extensive and varied in each instance
Petechial hemorrhage	7	
Larger intracerebral clot	3	
Subarachnoid hemorrhage	3	

The single case of chronic subdural hematoma had been drained through a small trephine opening. At autopsy the cyst cavity was still filled with semisolid and fluid contents. About three-fourths of the hematoma was semisolid. (When the hematoma is mostly semisolid, it should be drained through a small osteoplastic flap rather than through a single or two trephine openings. In the above case, the single trephine opening seemed inadequate.)

## EPIDURAL HEMORRHAGE

There were eleven cases of epidural hemorrhage of surgical proportions (about 30 Gm. and over) and an additional four cases of small hemorrhages in the epidural space.

The fronto-parieto-temporal region was the most frequent site among the larger hematomas (Fig. 7). There were eight cases in this group. A bilateral frontal hematoma was seen in one instance. A clot in the parieto-occipital region was present in one case, and a right cerebellar and right occipital localization was found in another (Fig. 8).



Fig. 7.—An example of acute epidural hemorrhage of representative size. This patient, aged 13 years, fell from a bicycle at 5:00 P.M., striking his head on a curb; he walked home, arriving at 6:30. A physician was called and the boy expired at 9:30 P.M.

The source of the hemorrhage was thought to be the middle meningeal artery in nine cases. The dural veins may have contributed to the clot. The frontal hematoma probably arose from venous and anterior meningeal artery bleeding. The clot in the cerebellar region was of lateral sinus origin.

The larger hematomas were intimately related with fracture except in one case. The fracture was depressed in one instance. It seems that

the position of the fracture is most significant in epidural hemorrhage, making it obligatory to search for the clot in its vicinity. The frontal epidural hematoma without fracture is extremely interesting. Its formation was possibly as follows: A separation of dura and bone may have been initiated by the trauma either by deformation of the cranial vault without accompanying deformation of dural membrane or by actual movement of the dura in the direction of the force when the moving head was suddenly stopped. The initial separation of the dura and bone would cause bleeding into the epidural space. With more bleeding, a further separation of the dura off the bone would ensue, the latter would expose more vessels to add to the bleeding, thus bringing about a vicious circle.

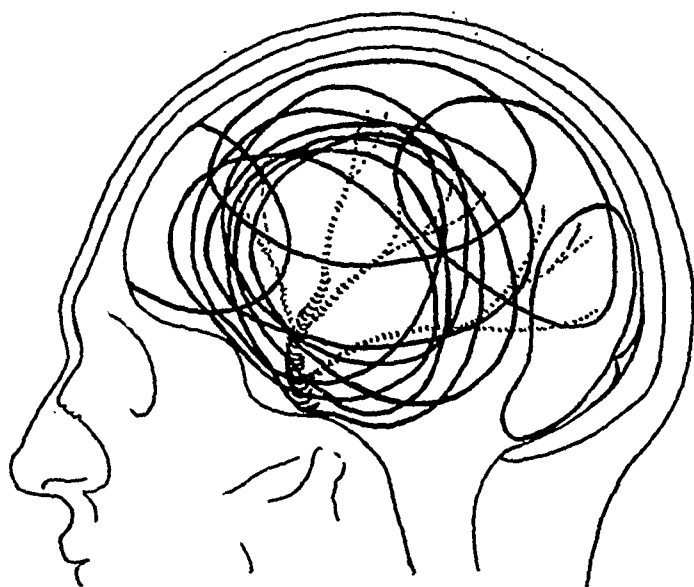


Fig. 8.—Diagrammatic representation of the cases of epidural hemorrhage in this series. Note that the greatest majority occur at the fronto-parieto-temporal region.

Cerebellar epidural hematoma is infrequently diagnosed before death except in puncture wounds of the lateral sinus region. Probably the profound associated lesions of the nervous system mask pure localizing signs. In the case described by Coleman and Thomson, there was a slow onset of stupor and eventual hypotonia and areflexia. A large posterior fossa clot was successfully removed. In selected cases, the site and type of fracture along with clinical evidences of increasing stupor may justify exploration of the posterior fossa for an epidural clot.

In this small group of cases, associated lesions in other parts of the nervous system were frequent. Purely on the basis of post-mortem examination, only two of the eleven cases could have been materially benefited by surgery. It is not surprising that a lucid interval was noted in only two cases.

## PETECHIAL HEMORRHAGES

Petechial hemorrhages recognized by gross examination were found to be present in fifty-four cases (Fig. 9). Small hemorrhages were seen in seventeen of the eighteen cases of bullet wounds of the head. Petechial hemorrhages were noted in the pons and in the medulla in a total of twenty-five cases. Twenty of these victims were struck by moving vehicles. Three of the hemorrhages were the result of falls. Six of the group with pontine and medullary lesions showed no fracture of the skull. Four cases of subdural hematoma had associated pontine and medullary lesions. Only six of the twenty-five victims survived the injury, the longest period of survival being thirty-three hours.

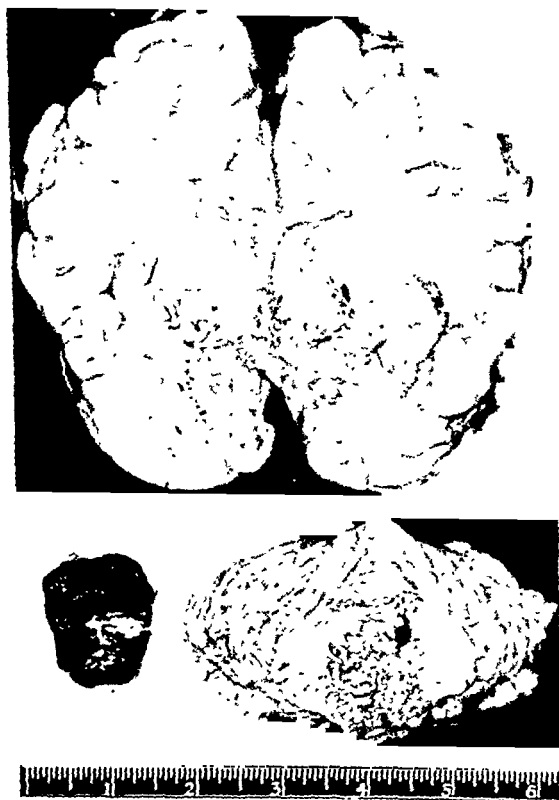


Fig. 9.—An example of unusually severe, diffuse, intracerebral hemorrhages (petechial) involving the brain stem and basal ganglia. This patient was dead on admission to the hospital following an auto accident (associated extensive skull fracture).

*Victims Dead on Admission.*—An analysis of sixty-one victims dead on admission is shown in Table VIII. Among the sixty-one cases, epidural hemorrhage was noted in 4, subdural hemorrhage in 13, subarachnoid hemorrhage in 18, petechial hemorrhages in 21, contusions in 25, and fracture of the skull in 39 cases. Associated injury elsewhere in the body

TABLE VIII

## ANALYSIS OF SIXTY-ONE VICTIMS DEAD ON ADMISSION

Pathology	
Epidural hemorrhage	4
Subdural hemorrhage	13
Subarachnoid hemorrhage	18
Massive intracerebral hemorrhage	0
Petechnal hemorrhage	21
Fracture	39
Contusions	25
Associated injuries	
Extremity injury	12
Abdominal injury	2
Chest injury	9
Vertebral column injury	4
Associated injury most important cause of death	9
Age (yr.)	
Under 5	2
5 to 10	1
10 to 20	7
20 to 30	7
30 to 40	8
40 to 50	14
Over 50	22

TABLE IX

## ANALYSIS OF THIRTY-NINE CASES WITH NO SKULL FRACTURE

Pathology	
Epidural hemorrhage	1
Subdural hemorrhage	9
Subarachnoid hemorrhage	16
Massive intracerebral hemorrhage	1
Petechnal hemorrhage	19
Contusions	13
Associated injuries	
Extremity injury	13
Abdominal injury	3
Chest injury	11
Vertebral column injury	2
Associated injury most important cause of death	9
Age (yr.)	
Under 5	0
5 to 10	0
10 to 20	2
20 to 30	3
30 to 40	9
40 to 50	12
Over 50	13
Duration of life	
Dead on admission	22
2 hr.	3
3 hr.	2
5 hr.	1
10 hr.	1
20 hr.	3
30 hr.	1
2 days	1
4 days	1
5 days	0
Over 5 days	4

was common. The age distribution showed the usual pattern of higher mortality in the older age group.

*Cases With No Skull Fracture.*—In Table IX the cases with no skull fracture are analyzed. Among thirty-nine such cases, one had epidural hemorrhage and nine showed subdural hemorrhage. In sixteen, there was subarachnoid hemorrhage; in nineteen, petechial hemorrhages; in thirteen, contusions of the brain surface. One case had a rather large intracerebral clot. The age distribution again showed the usual pattern of greater numbers among the older people. The duration of life following trauma has been analyzed for the group. It is noted that twenty-two were dead on admission, and an additional ten died within thirty hours after injury. Amazingly extensive intracranial lesions were frequent.

The question of so-called primary shock causing death may be raised in connection with the cases with no fracture who died soon after injury. Although in a few cases the pathologic changes were slight, intracranial lesions were invariably present in every instance.

*Concomitant Injuries.*—Associated pathologic lesions other than cerebral were held responsible for deaths in seven of ninety-four cases with fracture of the skull and in nine of thirty-nine cases in which there was no fracture present. In the thirty-nine instances of trauma without fracture, there was associated injury in twenty. Thus, nineteen instances of death occurred without fracture of the skull and without contributive injury, due solely to the intracranial disturbance. The associated lesions in the twenty cases with no skull fracture are given in Table X.

TABLE X  
CONCOMITANT INJURIES

INJURY	NUMBER OF CASES
Chest	5
Chest and abdomen	1
Abdomen and extremities	0
Extremity	6
Extremity and chest	4
Abdomen	1
Abdomen, chest, and extremity	1
Fracture vertebral column	2

*Clinical Pathologic Correlations.*—Seventy-two of the patients in this study reached the hospital after injury. Twenty-two were dead at the time of admission. The remaining hospitalized fifty were distributed among twenty-two hospitals in the Detroit area. The clinical records of these patients were studied in light of subsequent pathologic findings. The length of life, following hospital admission, varied from a few minutes to twelve days. Twenty-six of the group died in twenty-four hours or less after admission. Thus, complete neurologic study was, at times, impossible. In most instances the information contained in the records was incomplete. However, certain findings stand out and are worthy of mention.



Thirty-five patients were unconscious at the time of admission and continued in coma; five were semiconscious and became unconscious; ten showed lucid intervals, either reaching consciousness after being unconscious and lapsing again into stupor (four) or being conscious and then becoming unconscious (six). Among the ten patients with the state of consciousness suggesting a progressive lesion, a subdural or epidural hemorrhage was the cause of death in four cases. (Two of these were operated upon.) In four of the patients there was diffuse brain injury associated with skull fracture; in two, fatty cerebral embolism (Fig. 10) was the cause of death.

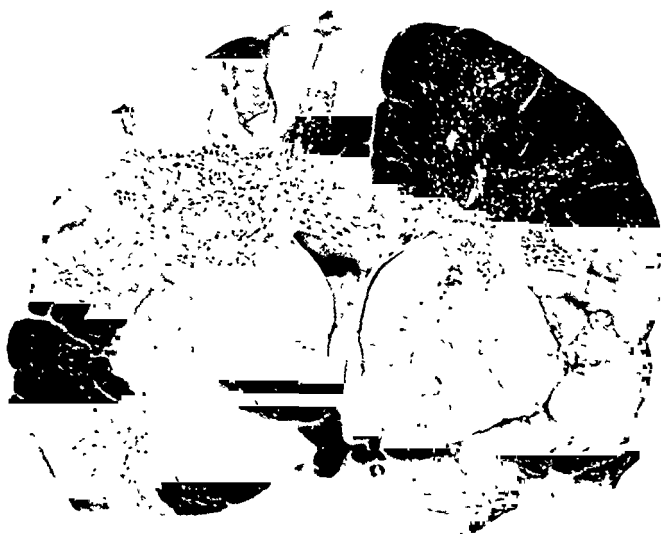


Fig. 10.—An example of cerebral fat emboli complicating head injury. There were fractures of both tibias and a lucid interval of 18 hours. The spinal fluid was slightly bloody with a pressure of 330 mm. of water. The patient was explored for subdural hemorrhage.

Patients were described as being in shock in but two instances. The blood pressure on admission was 84/50 and 60/40, respectively. The blood pressure was low in two other cases (90/0 and 80/54). In one there was associated severe injury to other parts of the body. The greatest majority of those with profound head injury showed no remarkable change in blood pressure and pulse throughout their stays in the hospital.

Hemorrhages from the ears, nose, and mouth were commonly reported in the hospitalized group. Such findings were present in twenty-four of the group of fifty.

Neurologic data were meager, and only gross abnormalities appeared to be reported. Focal signs of paresis, paralysis, or pyramidal tract disturbance were present in thirteen cases. In five instances the signs were bilateral. Seven of those showing focal signs were patients with subdural or epidural hemorrhages. In the hospitalized group, there were seven

subdural, four epidural, and one case of epidural and subdural hemorrhage, a total of twelve. Six of the twelve were operated upon.

Examinations of the pupils were reported in twenty-seven patients. Unequal pupils were present in thirteen instances, five of these in patients with subdural or epidural hemorrhages. One or both pupils were fixed to light in ten instances; in four, the examination was normal.

Correlation of the available information as related to the terminal states of the patients was not suggestive of characteristic clinical patterns associated with characteristic pathologic lesions. Thirteen patients died with temperatures ranging from 105 to 109° F. In five, medullary lesions were present. Respirations were elevated to above 40 per minute in twenty-one cases, four of which showed petechial hemorrhages in the medulla. In five patients, the respirations remained below 20. The most prominent and puzzling feature of the "neurogenic" pattern of death was the tachypnea with or without pulmonary edema.

#### DISCUSSION

The physical forces producing craniocerebral injuries are varied but may be grouped into the following five general classes: (1) force applied to a relatively fixed head (direct blow); (2) force applied to a nonfixed head which may move by the force (direct blow); (3) force produced by the head in motion coming in contact with a nonmoving or slower moving object (indirect blow); (4) a combination of the preceding circumstances, occurring particularly in auto accidents; (5) in indirect blows, the intracranial contents moving in the direction of the force, may abut against more solid structures, producing bruising of the brain surface (Koehler). Similarly, the "crowding together" of the various portions of the brain itself, because of differences in density, may result in parenchymatous lesions. Contrecoup lesions so common in head injury (Fig. 11) are ascribed to a lag of the brain behind the more rapidly moving cranium, causing the contents of the skull to abut against bone. Another viewpoint worthy of mention is the possible "bouncing back" of the brain when the moving head is suddenly stopped by a nonmoving or slower moving object. Evidence for these conclusions was found in the autopsy material studied.

Contusions and bruises of the brain surface were more frequent on the orbital surfaces of the frontal lobes and at the junction of the frontal and temporal poles of the hemisphere on one or both sides. The higher incidence of bruises in this neighborhood may be due to the many bony irregularities against which the brain rests. The irregular base of the anterior fossa and the sharp edge of the lesser wing of the sphenoid serve as abutments for the brain in motion. Tears and contusions may ensue in these areas following sudden arrest of the brain. When the direction of the blow causes the intracranial contents to move posteriorly, the tentorium cerebelli may accomplish much in protecting the brain. Contusions of the more posterior portions of the brain were infrequent, we believe, because of the "buffer" role of the tentorium. In the dog,

the osseous tentorium has no "give" as is the case in the human. Therefore, it is reasonable to expect that a higher incidence of injury would obtain in the occipital regions in the animal. In the human being, since a majority of the contusions occur on the anterior third of the brain surface, it is no wonder that most of the cases of subdural hemorrhage occur in the fronto-parieto-temporal regions.

The occurrence of multiple petechial hemorrhages associated with cranial trauma has been frequently noted and commented upon (Cassasa, Vance, Martland, and Beling). Aside from those caused by emboli (fat embolism, endocarditis, etc.), petechial hemorrhages are probably brought about by a combination of trauma and pathophysiologic changes. The "crowding together" of the various portions of the brain may cause parenchymatous damage due to "squashing." The resultant localized area of damage interferes with the normal nutrition and capillary-tissue



Fig. 11.—An example of contrecoup injury to the cortex opposite the site of a depressed, fractured skull.

exchange of the region, causing stasis, necrosis, and hemorrhage by diapedesis. It is well known that petechial hemorrhages may occur without trauma (usually preterminal). In such cases due to alteration in blood supply of the brain, a vascular stasis with anoxia may cause areas of necrosis eventuating in small hemorrhages by diapedesis and vessel wall damage. Of interest is the finding of petechial hemorrhages in the spinal cord in experimental head injury (Jakob, Denny-Brown).

Of the total group of 151 cases studied, there were twenty-two instances of acute subdural hematoma, eleven cases of epidural hemorrhage, and one case of chronic subdural hematoma, representing in their total, 21.5 per cent of the entire group. These thirty-four lesions were of sufficient size to classify as operable in type. Vance found that 26.2 per cent of the patients of 507 autopsied cases died as a result of either

subdural or epidural hemorrhage. Munro reported these types of surgical lesions in 20.8 per cent of 1,203 cases of head injury. One must conclude that hemorrhage producing a cerebral mass lesion is of frequent occurrence following trauma. When unassociated with profound intracerebral injury, the results of surgical treatment are highly satisfactory. Accompanying bruising of the brain, petechial hemorrhages or both occurred frequently as previously noted. This fact is an important consideration in management.

Analysis of this group showed that while fracture of the skull was present and was on the side of the lesion in all of those patients with epidural hemorrhage, fracture was commonly absent in the subdural hematoma class. In eight instances it was found that the subdural hematoma was on the opposite side to the fracture. While roentgen studies would be of assistance in localizing the epidural hemorrhage on the basis of the site of fracture, this would not hold in the subdural hematoma group.



Fig. 12—An example of traumatic intracerebral hemorrhage of the massive type. The patient, aged 23 years, was struck by an automobile, and lived 8 hours; conjugate deviation of eyes to side opposite lesion; had cycles of relaxation followed by clonic movements of all extremities which changed into "a definite extensor tonic convulsion." Bilateral pyramidal signs were present.

Massive intracerebral clot was present in one case in this review (Fig. 12). It was in the temporosphenoidal lobe. Such localization is the commonest of subcortical clots of larger size. They occasionally accompany middle meningeal hemorrhage (Apfelbach). The clinical studies of Courville and Blomquist and Pilcher suggest that massive intracerebral clots occur more frequently than seen in this study, and such lesions may escape early recognition. Later they may cause symptoms leading to their exploration. However, most surgical lesions of the intracranial

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otic pressure would cause transfer of tissue fluids into the subarachnoid bed. A combination of the above is probably operative in a great many of the cases.

Traumatic edema of the brain was attributed by Cannon to increased osmotic pressure of brain tissue caused by extravasation, contusions, small thrombi, and necrosis. Courtney suggested that transudation of fluid about and into areas of laceration and bruises is the cause of brain edema. He felt that the process is similar to the edema about an inflammatory lesion elsewhere in the body.

Because the microscopic appearance of edema (increased tissue spaces between cells with many dead and dying cells) occurs not only about actual lesions but also in distant portions of the brain, other explanations have been sought for the generalized process. Vasomotor paralysis of cerebral vessels by trauma (Courtney) with subsequent venous stasis and tissue waterlogging, due to increased permeability of the capillaries, has been considered a possibility (Ricker). An initial localized edema may compress the brain, altering its nutrition; thus, a localized edema may be enhanced by anoxemia and anoxia and eventuate in generalized edema of the brain due to venous stasis, increased capillary permeability, and eventual tissue waterlogging (Schaller). Probably more than one factor is in operation. Increased osmotic pressure of the brain and spinal fluid with edema in conjunction with the lack of proper oxygen supply may be the basis for the generalized swelling of the brain in the absence of extensive intracranial hemorrhage.

Other explanations of increased intracranial pressure without severe hemorrhage are irritation and stimulation of the choroid plexus (Rand and Courville), with increased cerebrospinal fluid formation or the lowering of the rate of absorption of the spinal fluid due to venous stasis and increased venous pressure well above that of the cerebrospinal fluid (Jorns, Haussler, and others). In this connection, Weed felt that increased protein content in the cerebrospinal fluid due to blood retarded its absorption. It has long been suggested that there is traumatic internal hydrocephalus in many cases of fatal injury to the head. Jackson, and Shapiro and Jackson, in post-mortem studies, have recently re-emphasized the presence of increased intraventricular fluid and internal hydrocephalus in cases of head injury.

Among others, Haussler and Jorns distinguished between swelling and edema of the brain. Recently, Pilcher, Shapiro, and Jackson studied the water content of traumatized brains. They did not find any increase in water content. This suggested that the brain swelling was not due to edema. Shapiro and Jackson found an increase of extra- and intravascular blood content of the brain. This factor, as well as increased intraventricular fluid, was considered the basis for brain swelling by these authors. The cause for the swelling in cases of minimal hemorrhages is obscure. To what extent post-mortem findings of the

contents caused by trauma are found on the surface of the brain and intracerebral clots of surgical size are rare.

The significance of the presence or absence of a fracture of the skull in assessing the degree of cerebral injury is well brought out by this review.

The presence of a fracture has been repeatedly considered of major prognostic significance. It has been used as a criterion as to whether a patient should be hospitalized and for how long. In all probability it is true that a fracture of the skull is a rough index of the severity of the trauma. Associated damage to the intracranial contents is more common among the patients with fracture than those without bone injury. However, the absence of a fracture does not rule out severe and at times fatal intracranial injury. In 151 examinations, there were thirty-nine with no fracture of the skull. Of the thirty-nine cases, there was no associated injury in nineteen. Thus, these nineteen patients died solely of traumatic intracranial lesions. Particularly with the indirect type of injury to the head, the movement of the brain in the cranial cavity may produce contusions and tears or may result in profound intracellular damage. The presence or absence of a fractured skull as a criterion for the evaluation of the degree of cerebral injury would seem to be a loose standard.

The importance of concomitant injuries in influencing the outcome of the patient with cranial trauma was shown in this study. With indirect blows and particularly with injuries of great violence, not only may the head be struck, but also other portions of the body as well. In this study, associated pathologic lesions elsewhere than in the head were believed responsible for death in seven of ninety-four patients with skull fracture and nine of thirty-nine patients in whom no fracture was present. Early knowledge of the presence of such secondary injuries appears to be of major importance. The condition which mainly obscures the diagnosis of commonly encountered chest, vertebral, abdominal, and pelvic injuries is the unconsciousness of the patient with a centering of interest to the head.

Although this is primarily a discussion of gross findings in a series of necropsied cases, it would not be complete without a few words concerning increased intracranial pressure. Increased intracranial pressure has been attributed to edema of the brain, hemorrhage of intracranial contents, and increased intracranial blood volume due to trauma (Shapiro and Jackson). That hemorrhage into the intracranial contents can and does cause increased intracranial pressure is accepted. This is brought about by an actual increase in the volume of the intracranial contents by the escape of blood, or the bleeding, particularly into the subarachnoid spaces, may increase the osmotic pressure of the spinal fluid (Howe, Parker and Lehman) by increasing its protein content. Increased os-

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fluid content represent the true premortem conditions in the brain is also not clear. Alexander and Looney have raised many interesting questions in this connection. They reported that the amount of post-mortem water content of the brain was not a true index of edema or swelling.

That increased intracranial pressure due to trauma is a clinical entity is universally accepted. That some brains look swollen at autopsy, even though the subarachnoid spaces are obliterated (thus making the brain surface appear dry), cannot be denied. In occasional instances we have observed large amounts of fluid in the subarachnoid and subdural spaces. An acceptable viewpoint is one which does not deny the occurrence of edema and yet does accept that it may be present in some cases, due to the time of death, to treatment prior to death, and to a different set of physicochemical factors operating in a given case.

Although the pathologic findings in some of the cases in this series were minimal, all showed gross abnormalities. Death from so-called concussion\* was not seen in this series. Examination of the clinical material available showed also that the occurrence of shock was infrequent if not unusual in uncomplicated cases of head injury. Increasing pulse rate with lowering blood pressure and other characteristic signs of shock were reported in only two instances among the clinically observed group. The physiologic state present in those patients who died instantly or immediately following trauma can only be conjectured upon. Of twenty-two victims who were dead on admission to the hospital, all but two showed severe pathologic damage to the brain and fractures of the skull. There were three instances of subdural hematoma.

#### SUMMARY

1. In practically every instance of fatal head injury there is a combination of pathologic processes. For example, although the chief lesion may be an epidural hemorrhage, petechial hemorrhages and cerebral bruises frequently coexist.

2. There is great variation in the extent and severity of brain lesions in the fatal cases. Among some, few pathologic lesions were noted to explain the cause of death. However, in every case, gross lesions were found.

3. A massive intracranial hemorrhage due to trauma is usually on the surface of the brain and may be amenable to surgical treatment. Large intracerebral clots are rare.

4. In epidural hemorrhage, exploration about a fracture line seems justifiable. In subdural hemorrhage, a fracture line is of little value in localization, often being opposite to the side of the subdural hemorrhage.

\*The term concussion is used in a most elastic manner by different authors. As understood in this paper, concussion is characterized by an unconscious state after head injury unassociated with macroscopic or microscopic lesions of the brain.

Both legs were slightly spastic, but strength appeared to be normal in all muscle groups. There was no atrophy, and fasciculations were not seen. Sensory examination revealed a fairly sharp level at the upper border of the eleventh thoracic dermatome bilaterally, below which there was anesthesia and marked hypalgesia extending down to include the third lumbar dermatome. From the fourth lumbar to the second sacral dermatome the hypalgesia was less marked, and light touch was appreciated. Over the buttocks the sensory loss was not symmetrical: on the right there was moderate hypesthesia and hypalgesia, whereas on the left light touch was not appreciated at all, but pinprick produced an intensely painful sensation which was poorly localized. Position sense was markedly impaired in the toes bilaterally, and vibratory sense was absent below the knees. In placing the heel on the knee he showed slight sensory ataxia. His station was unsteady with eyes closed, and his gait was moderately ataxic. The abdominal reflexes were present except for the left upper, which could not be obtained. The knee and ankle jerks were hyperactive bilaterally, and there was sustained ankle clonus on the left. The plantar responses were extensor in type.

Examinations of the urine and blood showed no abnormality, and the blood Wassermann was negative. The spinal fluid was clear and colorless. The initial pressure was 110 mm. of water. Manometric tests performed according to the standardized technique of Grant and Cone<sup>1</sup> suggested partial subarachnoid block. The first specimen of fluid removed gave a strongly positive reaction for protein (Pandy test), whereas the final specimen gave a negative reaction. The fluid contained no cells. The Wassermann and colloidal mastic tests were negative.

Roentgenograms of the spine showed scoliosis to the right starting at the tenth thoracic vertebra and extending to the fourth lumbar, with rotation of the bodies of the lumbar vertebrae to the right. There was partial spina bifida of the first sacral segment with the right lamina lying about 8 mm. beneath the left lamina. The lumbosacral articulations could not be distinctly seen. After injection of 2 c.c. of iodized oil (Lipiodol) into the cisterna magna, fluoroscopy and films revealed a marked delay in the passage of the oil at the level of the eleventh thoracic vertebra, the oil passing in a thin stream to the right of an apparent obstruction.

Following lumbar puncture the patient complained of a slight increase in his original symptoms, and examination revealed more pronounced sensory loss over the segments previously involved. A tentative diagnosis of intramedullary tumor at the level of the eleventh thoracic vertebra was made, and he was transferred to the neurosurgical service.

*Operation.*—A midline laminectomy incision was made over the lower thoracic spines. The spinous process and laminal arch of the eleventh thoracic vertebra were resected. On opening the dura an extensive soft arachnoiditis was noted. Just below the level of the dural incision a rounded, yellow mass could be seen, apparently lying within the conus medullaris. The spinous process and laminal arch of the twelfth thoracic vertebra were then resected, and the laminal arch of the first lumbar vertebra was beveled slightly, giving a dural exposure about 7 cm. in length. On extending the dural incision a very striking picture was seen (Fig. 1). A well-demarcated, yellowish-white tumor mass filled the conus medullaris, coming to the surface on the left dorsal aspect of the cord, covered only by a thin layer of pia-arachnoid membrane. The tumor measured 3 cm. in length and 1.5 cm. in width and depth, the upper pole being at about the level of the third or fourth lumbar segment of the cord. It was slightly nodular. The entire mass was gently dissected out of its bed in the cord, and no clearly defined membrane could be seen surrounding it. It appeared to be a cholesteatoma. When dissection was completed, there was no evidence of a cyst wall or of any tumor tissue remaining in the pocket.

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# A CASE OF EPIDERMOID TUMOR OF THE SPINAL CORD

## REVIEW OF LITERATURE OF SPINAL EPIDERMoids AND DERMoids

ROBERT L. CRAIG, M.D., DURHAM, N. C.

(From the Neurologic Service of Duke Hospital and the Department of Internal Medicine, Duke School of Medicine)

**I**NCLUSION cysts developing in relation to the spinal cord and its meninges are rare in the experience of most neurologists and neurosurgeons. The standard textbooks make scant reference to these tumors, but in the periodic literature one finds a sufficient number of case reports to establish them as a not uncommon clinico-pathologic entity. On the basis of gross and histologic characteristics three distinct types are recognized: (1) the epidermoid or cholesteatoma, containing only epidermal tissue and its debris; (2) the dermoid, containing, in addition, dermoid structures and derivatives; and (3) the teratoma, containing tissues derived from two or more germinal layers. The case reported here is believed to be an example of the first type.

### REPORT OF A CASE

*History.*—W. M. (A-55912), a 25-year-old white male, referred to Duke Hospital with a tentative diagnosis of "spinal cord tumor," was admitted to the neurologic service, Feb. 12, 1941. He complained of low back pain and numbness, tingling and stiffness in his legs of five months' duration. His general health had always been excellent. There was no history of injury. Since early childhood he had had what he called "growing pains" in the thighs, occurring at night after strenuous work or exercise. He also described infrequent attacks of a rather sharp pain in his lower thoracic spine radiating toward the left scapula, brought on by jarring or suddenly turning the body to either side. In October, 1940, or about five months before admission, he began to notice on going to bed a dull, poorly localized ache in the lower part of the back which would keep him awake for several hours, together with numbness and tingling in the anterior thighs, first on the left and later bilateral. He had sometimes awakened during the night with uncertainty as to the position of his feet in the bed. At first he did not notice these symptoms during the day, but gradually they became more constant. The numbness and tingling spread downward to the feet. About four months before admission he began to notice slight hesitancy in initiating urination. Stiffness of the legs developed gradually, and his gait became unsteady. Following a lumbar puncture on February 7, he noticed for the first time slight weakness of his legs, causing increased difficulty in walking. He had lost twenty pounds in weight.

*Examination.*—Physical examination revealed an undernourished young man with poor muscular development, who did not appear acutely ill. A general glandular enlargement was present, the nodes being hard and nontender. Examination of the back with the patient standing disclosed obliteration of the normal lumbar curvature and a moderate scoliosis, with convexity to the right, involving the lower thoracic and lumbar spine. There was no localized deformity or tenderness of the spine.

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seen grossly and no hairs were present. Microscopic study of several serial sections taken from one of the larger fragments, stained with hematoxylin and eosin, showed what appeared to be a multiloculated cyst with numerous invaginations and outpouchings of its wall (Fig. 2). The cyst wall appeared as a crumpled purselike membrane composed of two or more layers of well-preserved basal cells. Inside this basement membrane, and closely attached to it, were several layers of desquamating squamous cells which had lost their nuclei. These merged with an amorphous, vacuolated, necrotic substance in which the only recognizable cells were red blood cells, apparently from operative bleeding. Outside the membrane there was no supporting tissue, only scattered bits of tissue which, when stained with Mallory's phosphotungstic acid hematoxylin, appeared to be composed of interlacing fibers and large nucleated cells resembling nerve cells. It was thought that these might represent small pieces of spinal cord substance which had adhered to the basement membrane during removal of the tumor. No glands or hair follicles were seen in any of the sections. There was no evidence of malignant change. In a frozen section stained by Herxheimer's scarlet red the amorphous substance was found to contain numerous globules of fat. With the polarizing microscope, doubly refractile crystals characteristic of cholesterol were identified (Fig. 3). The pathologic diagnosis was "epidermoid of spinal cord."

#### DISCUSSION OF CASE

It is worth noting that this patient had had symptoms referable to his lesion since early in childhood. This fact, together with the finding of spina bifida of the first sacral segment, should have raised the suspicion of a congenital lesion. Spina bifida of the sacral segments is not an unusual finding in patients without neurologic complaints, but in this case the fact that the corresponding segment of the cord was involved by the tumor makes it highly probable that the two conditions were embryologically related. The sensory level was at the eleventh thoracic dermatome, and the upper pole of the tumor was at the level of the eleventh thoracic vertebra or at the third or fourth lumbar segment of the cord. The cutaneous sensory loss between the eleventh thoracic and third lumbar segments, therefore, must have been due either to compression of the nerve roots or to the arachnoiditis which was present. The tumor occupied a cleft between the posterior columns of the cord, lying slightly to the left of the midline. Practically its entire dorsal surface was exposed, being covered only by the pia-arachnoid. It must, therefore, be classified as subpial rather than intramedullary. Histologically this tumor was quite remarkable in that the basement membrane did not form a definite cyst wall but was folded up within the substance of the tumor; in places it was impossible to say whether the desquamating epithelium was on the inside or on the outside of the membrane. This suggests that the membrane was actively proliferating but did not have room to expand, with the result that it became folded on itself, entrapping between its folds desquamating squamous cells on one side and spinal cord tissue on the other. If fragments of spinal cord substance were removed with the tumor, as the sections suggest, this would adequately explain the postoperative development of paraplegia and the unsatisfactory surgical result.

ing daily catheterization. Within the first week he showed slight return of motor function in the right leg. On the eleventh postoperative day he began to void spontaneously. He continued to improve slowly, regaining some function in all muscle groups of the right leg and ability to move the left toes. There was also some return of sensation. He was discharged on the twenty-eighth postoperative day. He returned to the outpatient clinic approximately six months after operation, reporting slight improvement during the first two months but none since then.

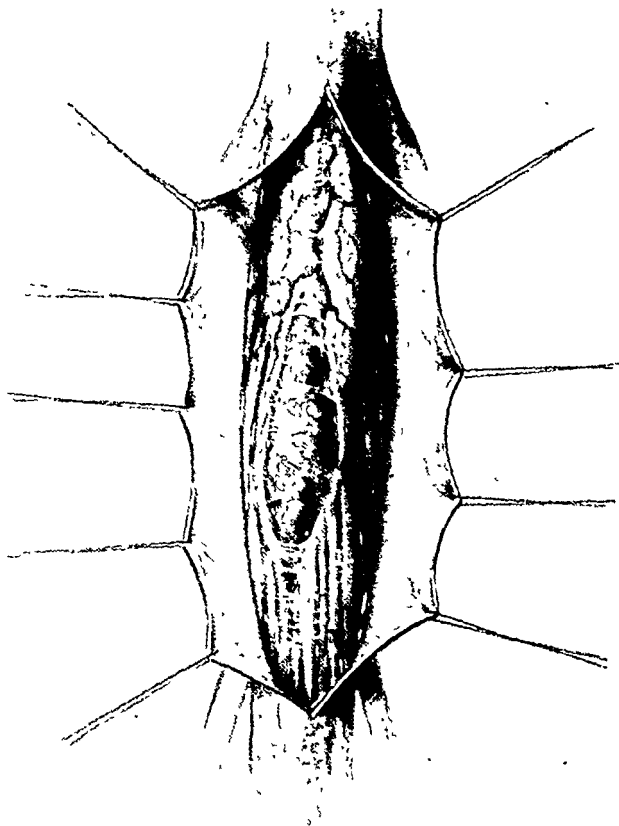


Fig. 1.—Drawing of operative field after retraction of the dura. The main body of the tumor lies in the conus, covered only by a thin membrane of pia-arachnoid.

He was unable to walk, except with crutches. He complained of hesitant micturition and complete impotence. On examination he was found to have a spastic paraplegia with little useful function in his legs and marked reduction in all forms of sensation below the tenth thoracic dermatome. His condition appeared to be stationary, and no further change was anticipated. His physician reports that he has subsequently returned to work at a sedentary job.

*Pathologic Study.*—Grossly the specimen consisted of several small pieces of soft, friable, cheesy material of a yellowish color, in which small lumps of a slightly firmer consistency could be felt. No encapsulating membrane could be

## REVIEW OF LITERATURE

The reported cases of dermoid and epidermoid tumors of the vertebral canal have been reviewed by Critchley and Ferguson,<sup>2</sup> Gross,<sup>3</sup> Bradford,<sup>4</sup> and most recently by Boldrey and Elvidge.<sup>5\*</sup> The cases collected by Boldrey and Elvidge, in 1939, number thirty-seven, to which they added three of their own. These authors state that in all instances they

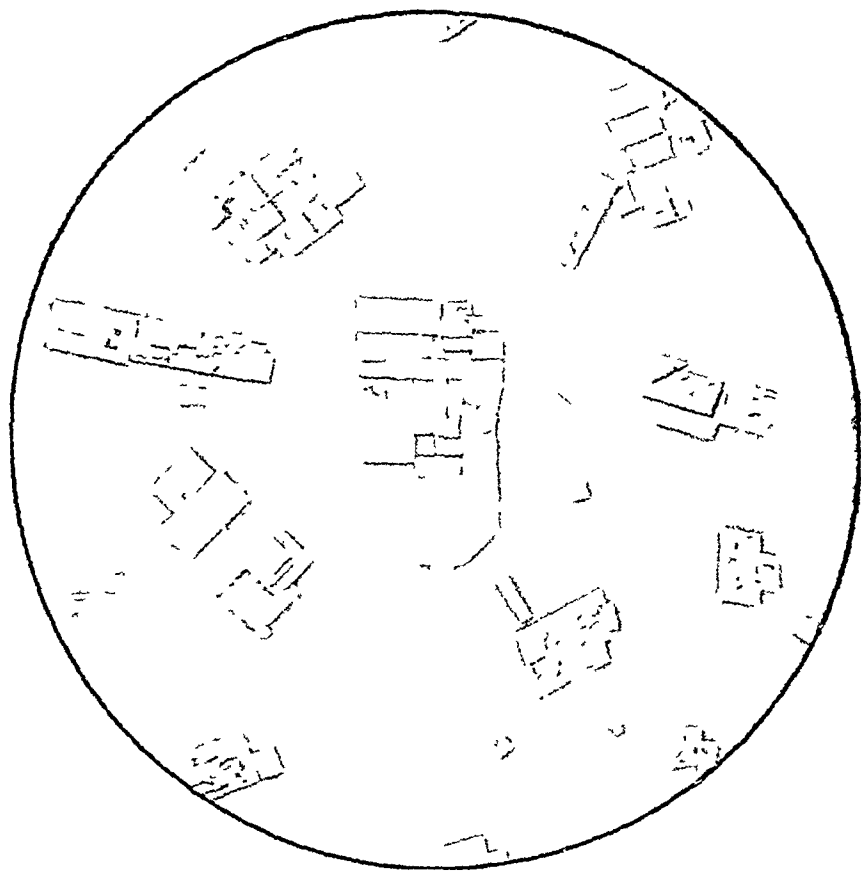


Fig 3.—Camera lucida drawing of doubly refractile cholesterol crystals, seen with the polarizing microscope, in a piece of formalin-fixed tissue from the tumor

have assumed the accuracy of the original pathologic diagnosis I have reviewed as much of this literature as is available and am unable to accept the following cases as either dermoids or epidermoids, for the reasons stated (The case numbers correspond with the enumeration in the authors' lists)

CASE 1 (Eppinger) —The only available reference to this case is in the review by Critchley and Ferguson,<sup>2</sup> and the data given are insufficient to make a diagnosis

\*A more recent review is to be published by Bagley and Arnold, who have kindly permitted me to read their manuscript.





Fig. 2A.—Photomicrograph showing low-power view of a portion of the tumor. The pedunculated nodule in the center of the field is covered by basement membrane, and its center consists of degenerative squamous cells and cellular debris. The material outside the membrane consists mainly of red blood cells, thought to be artifact resulting from bleeding at operation. (Hematoxylin and eosin stain,  $\times 43$ .)



Fig. 2B.—Photomicrograph showing tangential section. The invaginations of the basal cells represent small invaginations of the cyst wall.

stratified squamous epithelium cut in tangential section. The invaginations of the basal cells represent small invaginations of the cyst wall. (Hematoxylin and eosin stain,  $\times 160$ .)

and subdural dermoid cyst, similar to the case of Walker and Bucy described previously. Following an acute febrile illness diagnosed "meningitis," a 3-year-old boy developed rapidly increasing weakness of the legs. Examination disclosed spastic paraplegia and analgesia below the fifth thoracic dermatome. At the level of the ninth thoracic spinous process there was a cutaneous dimple from which hairs protruded. At operation a dermal sinus was traced from the dimple down to the dura, where it ended in a mass of distorted dermal structures and infected granulation tissue. Beneath the dura there was a large cyst compressing the cord to a mere ribbon. It contained desquamated epithelium, hairs, and debris. Its wall was composed partly of epithelium and partly of fibrous granulation tissue. Death occurred postoperatively.

Verbiest,<sup>15</sup> in 1939, reported a 65-year-old man who had had mild symptoms of spinal cord disease since the age of 12. All forms of sensation were impaired below the twelfth thoracic dermatome. The right leg was spastic, the left flaccid and atrophied. Lipiodol showed a block at the level of the twelfth thoracic vertebra. Laminectomy revealed chronic arachnoiditis and an intramedullary cyst. This contained gruelike material which by chemical analysis was found to consist of cholesterol, fat, and fatty acids. The capsule was composed of stratified squamous epithelium. Diagnosis: Epidermoid cyst. The patient developed post-operative sterile meningitis lasting four weeks. His condition was not improved by operation.

Bagley and Arnold<sup>16</sup> reported, in 1940, a 9-year-old boy with symptoms which brought him to an orthopedist, who found flexion deformities of the knees and hips, backward tilting of the pelvis, paravertebral tenderness, and muscle spasm. The only abnormal neurologic finding was a hyperactive right knee jerk. Lumbar laminectomy revealed a markedly tense dura, incision of which released a large amount of soapy material in which cholesterol crystals were identified. An encapsulating membrane was dissected away from the nerve roots, and microscopic study of this showed stratified epithelium beneath which there was a well-defined layer of connective tissue. Many hairs were found. The diagnosis was dermoid cyst and the patient was relieved of all symptoms.

This revision of Boldrey and Elvidge's collection brings to forty-two the number of reported cases in which critical analysis of the evidence justifies the diagnosis of dermoid or epidermoid tumor of the vertebral canal; an additional case is reported. In this review the dermoids and epidermoids have been grouped together, and this has been the tendency of all recent authors. The teratomas, or tumors containing derivatives of more than one germinal layer, are usually treated as a separate group and have been omitted. These tumors have been reviewed by Hosoi<sup>8</sup> and more recently by Masten.<sup>17</sup> To date fourteen cases have been reported.\* Cases of congenital dermal sinus, as discussed by Walker and Bucy,<sup>12</sup> have also been omitted except for those cases in which a definite dermoid cyst within the spinal canal has been demonstrated.

#### COMMENT

In the foregoing review no distinction has been made between the dermoids and the epidermoids, and it has been the custom of recent authors to group these together under the inclusive term "dermoids." While

\*Since the writing of this paper, L. A. French and W. T. Peyton (Arch. Neurol. & Psychiat. 47: 737-751, 1942) have reported two additional cases of teratoma and one of epidermoid tumor.

CASE 6 (Ivanoff).—The original article is unavailable. From the facts given in various reviews, this was apparently an anencephalic monster which died at birth and was found to have a malformation of the entire cerebrospinal axis. It cannot properly be classified as a tumor or cyst.

CASE 7 (Raymond, Alquier, and Coutellemont<sup>6</sup>).—In this case the principal lesion, a frontal lobe dermoid, was adequately proved. The multiple fatty lesions in the spinal meninges were apparently not studied microscopically but were assumed to be dermoids because of gross similarity to the cerebral lesion.

CASE 10 (Frick<sup>7</sup>).—This tumor contained bone marrow with myeloid cells and giant cells, calcium, connective tissue, hair, and blood vessels. It was reported as a case of teratoma and has been so accepted by Hosoi.<sup>8</sup>

CASE 13 (Elsberg<sup>9</sup>).—There is no pathologic description of this tumor. The author cites the case as one of questionable dermoid cyst, but the accompanying photomicrograph is labeled "gliomatous (?) cyst."

CASE 33 (Naffziger and Jones, Case 31<sup>0</sup>).—This tumor is said to have contained connective tissue, calcium, and a substance resembling cartilage. I am inclined to regard it as a teratoma.

*The following cases, either omitted or published subsequently, should be added to the collection of Boldrey and Elvidge.*

Craig and Mitchell,<sup>11</sup> in 1931, reported an 8-year-old boy with a history of intermittent back pain, nocturnal incontinence, and weakness of legs for three years. There was a dimple in the skin at the level of the fourth lumbar spinous process. Neurologic findings suggested tumor of cauda equina. At operation the dura was joined to the laminal arch of the fourth lumbar vertebra by a fibrous band. A subdural tumor compressed the conus and cauda equina. Diagnosis: Cholesteatoma. The patient has improved markedly.

Bouchut, Dechaume, and Michailidis reported, in 1932, a case reviewed by Bradford.<sup>4</sup> It was that of a 71 year old man with history dating back fifteen years, who came to autopsy and was found to have an intramedullary epidermoid of the conus medullaris. In addition there was dysembryoplasia of the adjacent portions of the cord and syringomyelic cavities.

Walker and Bucy,<sup>12</sup> in 1934, published a discussion of seven cases of congenital dermal sinus. The authors cite one case, originally reported by W. and N. Sharpe, in which such a sinus, chronically infected, was associated with an intradural cyst containing caseous material and hair. Although no pathologic report was given, the authors concluded that this was a dermoid.

Bradford<sup>4</sup> reported a case in 1938. This 3 year old boy had had symptoms for one year, and examination disclosed a flaccid paraparesis, perianal analgesia, and a palpable defect in the sacral lanuæ. The lumbar canal was markedly dilated. Operation consisted of incision and evacuation of an intramedullary cyst of the conus medullaris. The cyst wall was composed of simple, stratified, squamous epithelium. A mural nodule, however, contained hair follicles and sebaceous glands in addition to epidermis. The diagnosis was "dermoid cyst." The patient improved somewhat.

Masson,<sup>13</sup> in 1938, reported a 38 year old man with recurrent attacks of back pain and progressive neurologic disturbances for 17 years. There was spastic paraparesis with the sensory level at the ninth thoracic dermatome. Laminectomy revealed a "pearly tumor" at the eighth to ninth thoracic vertebra, lying between the pia and arachnoid on the dorsal surface of the cord. It contained hairs, and the pathologic diagnosis was "dermoid cyst." The patient was relieved of pain but the paraparesis became worse.

Walker and Moore<sup>14</sup> published an article in 1939. Although reported as a case of teratoid tumor, this appears to have been an instance of infected dermal sinus

he demonstrated by chemical analysis. He produced, furthermore, sterile meningitis experimentally by injecting fatty acids into the subarachnoid space of a dog. He did not go so far as to suggest that transverse myelitis might be caused by chemical irritants elaborated by the tumor, but in the light of the above mentioned cases this possibility is to be considered. In our own case it furnishes an alternative explanation for the postoperative paraplegia.

Spina bifida is not a frequent finding in the cases of epidermoid tumor, being reported in only two. One of these is the case reported here, in which the first sacral laminae were unfused. Since the tumor involved the corresponding segment of the cord, it seems likely that this represents an embryologic defect common to the spinal cord and vertebral column rather than a chance association. It is quite possible that the incidence of spina bifida would be higher if routine x-rays had been taken. In no case has a communicating dermal sinus been reported.

Epidermoids have been found at all levels of the spinal canal as high as the second thoracic vertebra; none has been reported in the cervical region. All have been intradural, with one exception, the case reported by Muscatello and cited by Boldrey and Elvidge.<sup>5</sup> Here the so-called epidermoid was an incidental finding, the principal lesion being an extradural dermoid with dermal sinus at a higher level. No pathologic details are given, and I have been unable to verify the original report. These tumors have been described as extramedullary in ten cases and as either intramedullary or subpial in nine cases. All of the latter have shown a definite connection with the pia. It is of interest that in two cases syringomyelic cavities have been found in the portions of the cord adjacent to the tumor, and in one case the entire central canal is described as abnormal.

Laminectomy was performed in fourteen of the cases of epidermoid tumor reviewed. Of these, eight were improved, although in two the tumor recurred. Six cases reported as improved had extramedullary tumors, and only two had intramedullary or subpial tumors. One case was reported as unimproved and two as worse; both of the latter were intramedullary tumors. There were two cases of postoperative death, and in one case the result was not mentioned. It appears, therefore, that the operative results, as in any other class of spinal cord tumor, depend largely on the position of the lesion in relation to the cord, being vastly better in the case of extramedullary lesions. As previously mentioned, the pathologic observations in the case reported here furnish an adequate reason for the poor results in dealing with intramedullary epidermoids, namely, the irregularity of the capsule with its many invaginations, including nervous tissue between its folds. For the same reason complete removal is rendered difficult, and recurrence is likely.

*Dermoids.*—The cases which I have selected include twenty-three dermoid tumors of the vertebral canal. In this group the onset of symptoms is considerably earlier than in the epidermoids. The first manifestation

this grouping is perhaps justifiable for purposes of historical review, considering that the published data often are insufficient to permit an accurate pathologic diagnosis, I feel that the clinical features and growth characteristics of the two types are sufficiently different to render separate discussion advisable. The following discussion is based upon an analysis of the clinical, operative, and pathologic findings in the forty-two cases comprising my revised collection of cases, and in the one reported here. Wherever possible, reference has been made to the original publications for details not mentioned in the reviews.

In differentiating between dermoids and epidermoids the criteria of Ewing<sup>18</sup> have been employed. He states that the simple dermoid consists of epidermis, dermis, and dermal derivatives, such as hair, glands, and sometimes teeth. It usually appears in the form of a cyst, commonly originating by the inclusion of a portion of ectoderm during the closure of embryonal fissures, or at the point of union between ectodermal and other structures. In the epidermoid, also known as cholesteatoma, definite dermal structures are wanting. This is a tumor composed of lamellated, waxy, or scaly material enclosed in a wall of stratified, squamous epithelium. It is regularly connected with the meninges. In both types disintegration of the epidermal slough gives rise to cholesterol crystals, which are found within the cyst.

*Epidermoids.*—Eighteen cases in the series are probably epidermoids; in two others the diagnosis of epidermoid is questionable but cannot be disproved, so they are included. The onset of symptoms occurred in the first decade in two cases, in the second in seven cases, in the third in four cases, in the fourth in three cases, and beyond the age of 40 in three cases. In one case the tumor was asymptomatic. The usual clinical course is that of any benign tumor of the spinal cord, except that paraplegia tends to develop more slowly. In two cases, however, the symptoms were intermittent and of rapid onset. In the case reported by Critchley and Ferguson<sup>2</sup> there was a history of cerebrospinal meningitis in infancy with complete recovery, transient paraplegia at 7 years of age, and rapid recurrence of paraplegia following an attack of influenza at the age of 15; the epidermoid was intradural but extramedullary at the seventh to eighth thoracic segments, and there was no evidence of encapsulation. Michelson's patient<sup>19</sup> had a history of paraplegia lasting six weeks after administration of a spinal anesthetic, followed three years later by a spontaneous episode suggestive of acute transverse myelitis; an extramedullary epidermoid lay on the posterior surface of the cord at the ninth thoracic vertebra. The observations and theories of Verbiest<sup>15</sup> offer a possible explanation for the occurrence of these acute and transient episodes. In his case, abstracted above, chronic arachnoiditis was found at the site of a subpial epidermoid, and after operation the patient developed a sterile meningitis lasting four weeks. The author suggested that this was due to liberation of fatty acids from the necrotic contents of the cysts, which

in detail by Bradford,<sup>4</sup> a 20-year-old woman had had pain in the scapular region one year previously, followed by symptoms of progressive cord compression. A draining sinus at the third thoracic vertebra, which was obstructed in places, communicated through a bifid spinous process with a large, extramedullary, dermoid cyst. The symptoms in this case were apparently due to obstruction of the sinus with dilatation of the cyst rather than to infection of the cyst itself. Hipsley's case, also reviewed by Bradford,<sup>4</sup> is similar. In the second case reported by Boldrey and Elvidge,<sup>5</sup> a man, aged 45 years, showed symptoms of a cauda equina lesion following immediately upon excision of an anal fistula six years previously. At operation a cystic tumor lay among the roots of the cauda equina and was attached by a cystic cord to the tip of the conus. Microscopically the cyst was a typical dermoid, while the cord was composed of loose glial tissue containing portions of an ependyma-lined lumen. The authors assumed that the cyst represented the original point of attachment of filum terminale to skin, that it was pulled upward by normal growth processes, and that radical excision of the anal sinus released intravertebral attachments and abolished external drainage. Here again there was no evidence of infection. In the third case reported by Boldrey and Elvidge, a child 2½ years of age had a pigmented spot at the level of the lumbosacral joint, present since birth, which had discharged intermittently for nine months. For five months the child had had recurrent attacks of meningitis. The only neurologic finding, except for signs of meningitis, was absence of the ankle jerks. An infected dermoid cyst filled two-thirds of the lumbar canal and communicated with the sinus, which passed through a bifid spinous process. Finally, the case of Walker and Moore,<sup>14</sup> abstracted previously, should be included in this group. Here the onset of paraplegia followed immediately an attack of meningitis, and the intradural cyst was chronically infected.

That dermal sinuses communicating with the spinal canal are rare is evidenced by the observation of Rogers and Dwight,<sup>20</sup> who stated in 1938 that in a personal experience with some 400 cases of pilonidal sinus they had not yet seen one communicating with the neural canal. However, on the basis of the seven cases reported by Walker and Bucy and the five cases mentioned here, I feel that its occasional occurrence should be kept in mind in dealing with cases of recurrent unexplained meningitis or transverse myelitis, and that the presence of a cutaneous dimple in the midline of the back or a discharging sinus should constitute an indication for radical surgical exploration. The condition occurs most commonly in infants, four of the six patients being between 2 and 3 years of age at the time symptoms developed. Involvement of the cord or cauda equina may occur in two ways. The sinus may become obstructed, causing sebaceous secretion to accumulate within the cyst, which then enlarges and compresses the nervous structures; or

appeared in the first decade in ten cases, in the second in five cases, in the third in four cases, and in the fourth in two cases. In two cases the age of onset is not given. Pain in the back and legs is the commonest early symptom, being mentioned in nine cases. This may be due to the fact that these tumors frequently occupy the lumbar portion of the canal where they tend to stretch the dura and nerve roots and may attain a considerable size before producing any neurologic deficit. In almost every case, however, symptoms of compression were present at the time of examination. Dermoids occur most commonly in the lower half of the canal, but one case of cervical tumor has been reported. In contrast to the epidermoids, they are oftener extramedullary than intramedullary, and in five cases the tumor has been entirely extradural. Only two cases of intramedullary dermoid have been reported. In three cases the tumor lay partly within and partly without the cord, spreading apart the posterior columns. In every case of extramedullary tumor the position has been dorsal to the cord. Spina bifida corresponding to the segmental position of the tumor has been reported in seven cases. Operation has been performed in nineteen cases with the following results: improved, nine; unimproved, two; recurred, 1; condition worse, 1; postoperative death, three; no mention, three.

A particularly interesting group of intraspinal dermoids are those associated with a congenital dermal sinus (pilonidal sinus). The pathogenesis and clinical features of these sinuses have been discussed by Walker and Bucy,<sup>12</sup> who reported the findings in seven cases which they had studied or had collected from the literature. A congenital dermal sinus, manifested externally by a small dimple in the midline of the back, discharges periodically serous or purulent material. The sinus extends to the meninges and its lumen acts as a pathway for infection to reach these structures. When this occurs, producing abscess formation, signs of meningeal irritation and weakness of the lower extremities develop. The spinal fluid, usually sterile, shows a pleocytosis. This malformation is usually associated with a spina bifida, but not necessarily so. The authors make no comment on the relationship of these sinuses to dermoid tumors within the spinal canal, and indeed in six of their cases there was no definite evidence of such a tumor. In one of their cases, however (Case 6, originally reported by W. and N. Sharpe), "A mass of caseous material containing hair was found imbedded between the dura and the left side of the spinal cord." No pathologic description of the tissue was given, but Walker and Bucy comment on the presence of hair at the base of the sinus as a "striking point." I am inclined to regard this finding as definite proof that they were dealing with an intradural dermoid cyst associated with an infected dermal sinus.

Among the reported cases of dermoid tumors of the vertebral canal I have found five similar cases, although in only two of these was there definite evidence of meningeal infection. In Ottonello's case, reviewed

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13. Masson, C. B.: Dermoid of the Spinal Cord: Report of a Case in Which There was Removal With Improvement, *Arch. Neurol. & Psychiat.* 40: 554-562, 1938.
14. Walker, A. A., and Moore, C. H.: Tumors of the Spinal Cord in Children, Report of a Case of Teratoid Tumor, *Am. J. Dis. Child.* 57: 900-906, 1939.
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17. Masten, M. G.: Teratoma of the Spinal Cord, *Arch. Path.* 30: 755-761, 1940.
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19. Michelson, J.: Cholesteatom des Rückenmarks, *Deutsche Ztschr. f. Nervenhe.* 127: 123-130, 1932.
20. Rogers, H., and Dwight, R. W.: Pilonidal Sinus, *Ann. Surg.* 107: 400-418, 1938.



the cyst itself may become infected from the outside, giving rise to a localized meningitis or subdural abscess. In either case the symptoms are of sudden or rapid onset, and they tend to be intermittent.

#### SUMMARY

1. A case of subpial epidermoid tumor of the spinal cord in the lumbosacral region is reported. The peculiar histologic appearance of the tumor, in which the basement epithelial membrane is thrown up into innumerable folds, possibly accounts for the unsatisfactory surgical result which was obtained.

2. The literature of epidermoid and dermoid tumors of the vertebral canal is reviewed, using the collection of reported cases made by Boldrey and Elvidge, in 1939, as a basis. This collection is revised by eliminating doubtful cases and adding others, and it is believed that forty-two cases of this type of tumor have been reported. The addition of the present case brings the total to forty-three, of which twenty are probably epidermoids and twenty-three are probably dermoids.

3. In general, the epidermoids and dermoids behave very much as do other types of spinal tumor in similar locations. Certain aspects of their symptomatology deserve special mention. In the case of the epidermoids, sterile inflammatory reactions such as meningitis and acute transverse myelitis occasionally occur. There is some evidence that these are due to fatty acids formed within the cyst and liberated into the subarachnoid space. Dermoid tumors are occasionally associated with congenital dermal (pilonidal) sinuses. Obstruction of such a sinus may result in sudden exacerbation of pressure symptoms. Infection reaching the meninges via these sinuses may give rise to septic meningitis or localized subdural abscess.

4. The preoperative recognition of these tumors is not always possible, but a history of symptoms beginning early in life, the finding of a cutaneous dimple or a discharging sinus in the midline of the back, or the presence of spina bifida corresponding to the involved segment of the spinal cord, should suggest that one is dealing with a congenital cystic tumor of epidermoid or dermoid type.

The author wishes to acknowledge the assistance of Dr. Barnes Woodhall and Dr. C. C. Erickson in the study of this case. Mr. E. H. Clark made the drawings.

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neath the skin flap through a posteriorly placed stab wound. The condition of the patient was good throughout the procedure and at the conclusion she was responding.

*Postoperative Course.*—Four hours after operation the patient was responding to questions and moving her left extremities weakly. For the first four days her general condition was good and she was quite bright, although the temperature rose as high as 103.6° F. There was copious drainage of slightly blood-tinged cerebrospinal fluid for the first forty eight hours, after which period the drain was removed. On the fifth postoperative day the patient vomited a feeding and shortly thereafter had a left-sided Jacksonian convulsion lasting an hour. Her lateral ventricle was tapped and deeply bloody fluid obtained. It was suspected that the vomiting attack had "blown" a thrombus out of the end of a small intraventricular vessel. For the subsequent week she was torpid and restless, complained of severe pain in her neck, and was irrational from time to time. The temperature ranged between 100 and

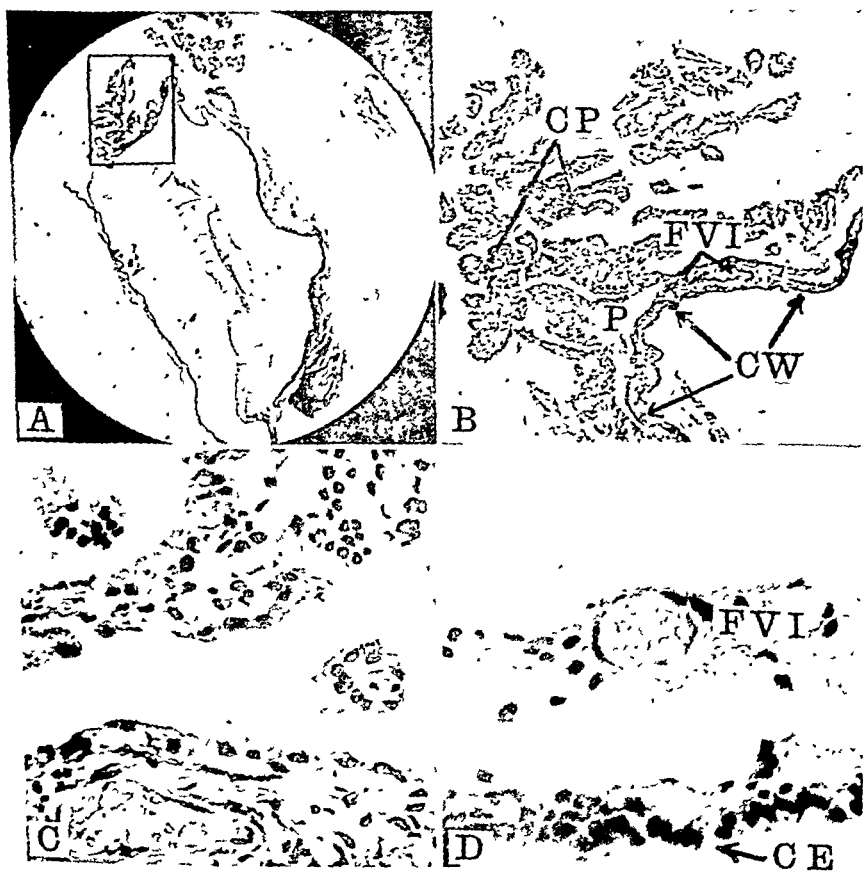


Fig 2—A, Cross section through the cyst enlarged about three times normal size. A small amount of homogeneously staining colloid material remains within the cyst.  
B, An enlargement of the outlined square in A. The attachment of the choroid plexus CP to the cyst wall CW is clearly shown. The fusion of the two layers of the fibrovascular investment FVI derived from the tela choroidea is shown at the pedicle of the tumor P. It will be noted that the epithelial lining of the cyst has two layers of fused tela choroidea enclosing it, as indicated by the arrows beneath the letters FVI.  
C and D are higher magnifications of the cyst wall. In C some areas of the epithelium are of columnar type. In D the typical single layer of ciliated cuboidal epithelium CE is shown.

to 60 per minute and she became so torpid that it was necessary to tap the ventricles several times during the night. The fluid was under considerable pressure and after each tap she improved for a few hours. Operation was performed as an emergency measure Aug. 31, 1941.

*Operation.*—The operation was performed using only procaine infiltration of the scalp. A moderately large, right frontal osteoplastic flap was reflected, the dura opened in a circular fashion from the base upwards, and the dural flap reflected over the longitudinal sinus. A vertical (dorsoventral) transectorial incision, 5 cm. long, was made two inches anterior to the Rolandic vein. The incision was carried down through the subcortex until the right lateral ventricle was entered. This was packed anteriorly and posteriorly with wet cotton to support the ventricular walls. Lighted retractors were introduced. The choroid plexus lying on the ventricular floor was identified and followed until it entered the foramen of Monro. The foramen was collapsed and appeared as a narrow slit below a thin, bulging septum lucidum. Because it appeared that it might be necessary to enlarge the foramen of Monro to gain access into the third ventricle, the terminal 1 cm. of the choroid plexus was coagulated with the electrosurgical unit. While the plexus was being handled with the bayonet forceps, traction was exerted slightly and for a moment a glistening tumor



Fig. 1.—Both lateral ventricles are widely dilated, the left more than the right. The arrow in A points to the sharply cut-off air shadow in the dilated foramen of Monro. The third ventricle is not visible in any position of the head. Both lateral ventricles were punctured and the fluid exchanged for air. The septum lucidum is intact.

appeared in the orifice of the foramen of Monro. The tumor was grasped with an other pair of forceps and with gentle teasing it was possible to slip the entire tumor through the foramen into the lateral ventricle. The tumor was about the size of a small cherry and appeared to be a thin-walled translucent cyst with fine vessels traversing the surface. It was attached to the portion of the choroid plexus within the third ventricle. This attachment was coagulated and cut. Slight bleeding followed from small veins about the foramen of Monro but these were controlled with cotton packs. Before withdrawing, the septum lucidum was punctured in order to insure drainage from the right to the left lateral ventricle, as it was anticipated that the right foramen of Monro might be blocked for a few days from edema. A thin split Penrose drain was placed within the lateral ventricle and brought out through a centrally placed incision in the dural flap which was tightly resutured in place. The bone flap was returned and wired into place and the drain led out be-

neath the skin flap through a posteriorly placed stab wound. The condition of the patient was good throughout the procedure and at the conclusion she was responding.

*Postoperative Course.*—Four hours after operation the patient was responding to questions and moving her left extremities weakly. For the first four days her general condition was good and she was quite bright, although the temperature rose as high as 103.6° F. There was copious drainage of slightly blood tinged cerebrospinal fluid for the first forty eight hours, after which period the drain was removed. On the fifth postoperative day the patient vomited a feeding and shortly thereafter had a left sided Jacksonian convulsion lasting an hour. Her lateral ventricle was tapped and deeply bloody fluid obtained. It was suspected that the vomiting attack had "blown" a thrombus out of the end of a small intraventricular vessel. For the subsequent week she was torpid and restless, complained of severe pain in her neck, and was irrational from time to time. The temperature ranged between 100 and

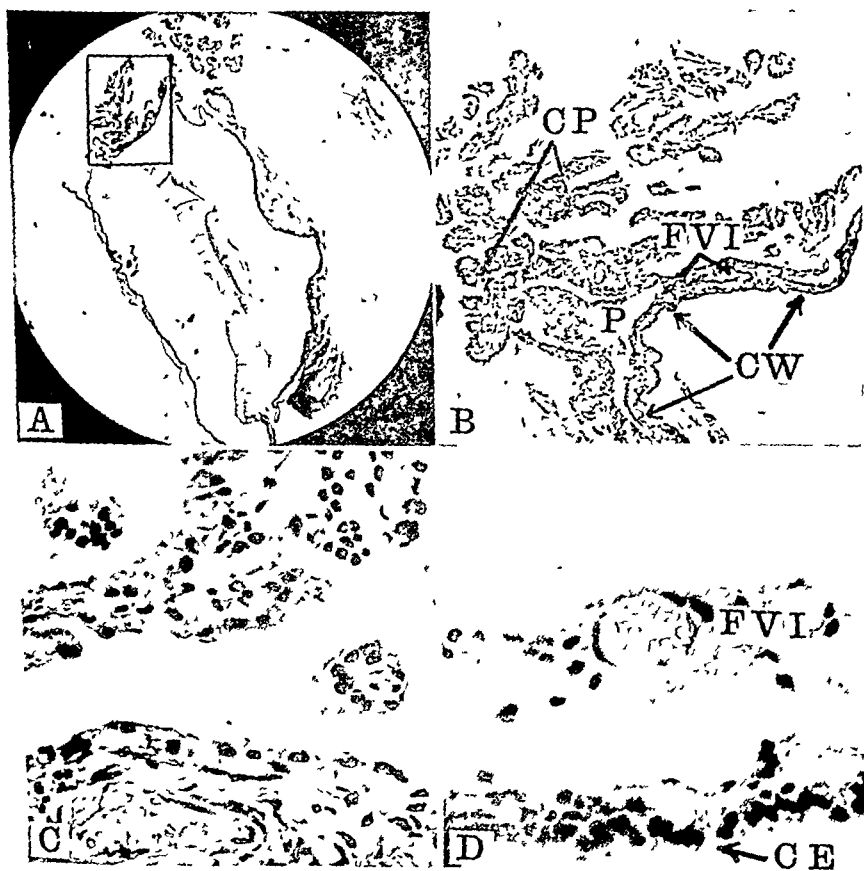


Fig 2—A, Cross section through the cyst enlarged about three times normal size. A small amount of homogeneously staining colloid material remains within the cyst. B, An enlargement of the outlined square in A. The attachment of the choroid plexus CP to the cyst wall CW is clearly shown. The fusion of the two layers of the fibrovascular investment FVI derived from the tela choroidea is shown at the pedicle of the tumor P. It will be noted that the epithelial lining of the cyst has two layers of fused tela choroidea enclosing it, as indicated by the arrows beneath the letters FVI. C and D are higher magnifications of the cyst wall. In C some areas of the epithelium are of columnar type. In D the typical single layer of cuboidal epithelium CE is shown.

102.6° F. but subsided gradually and became normal by the seventeenth postoperative day. At this time the ventricular and spinal fluid were xanthochromic. Indigo-carmin dye instilled in the right lateral ventricle was promptly recovered from the left ventricle and appeared also in the spinal canal in a few minutes. The power of her left extremities rapidly improved during the postoperative period, vision was returning and she became alert and cheerful. She was up in a wheel chair on the eighteenth day and walking on the twentieth. She was discharged twenty-one days after operation. At this time there was no gross weakness of the left extremities although a Babinski sign was present. The left angle of her mouth drooped slightly. The ocular palsies had disappeared and the papilledema was subsiding. She was able to read newsprint easily. Mental examination showed only a moderate psychomotor retardation and an unwarranted jocularity.



Fig. 3.—Photograph of the patient taken seven weeks after operation. The only residual neurologic sign at this time is a slight weakness of the left side of the face which is demonstrated by her smile.

Four months after operation, the patient had almost entirely recovered. She was taking full part in social activities and had returned to her farm work. Visual acuity was 20/20 in either eye and the visual fields appeared full. The fundi were normal with no evidence of optic atrophy. Neurologic examination was negative except for a slight weakness of the left angle of the mouth (Fig. 3). There were no complaints referable to the nervous system.

## PATHOGENESIS AND ANATOMIC CONSIDERATIONS

Paraphysial cysts are now recognized as arising from the paraphysial body, an ancient gland situated in the midline of the rostral portion of the roof of the third ventricle.<sup>11</sup> It is found in all vertebrates and reaches an especially high development in amphibians and reptiles.<sup>12</sup> Francotte<sup>13</sup> first identified its presence in the early human embryo. Krabbe<sup>14</sup> found that its evolution and involution was rapid, the structure first appearing at about the seventy-fifth day of gestation (20 mm. stage) and disappearing shortly thereafter. In some individuals, remnants of the gland apparently persist throughout fetal life and presumably enlarge slowly during postnatal existence by retention of the products of the secreting epithelial cells. Indeed, small and clinically insignificant paraphysial cysts have been observed as incidental findings at autopsy.<sup>14</sup> McLean<sup>7</sup> has fully described the life histories of these tumors. As they increase in size and become heavier, they sag downward upon the tela choroidea and in this way are eventually enfolded by the layers of the tela (Fig. 4). This intimate investment by the tela choroidea has led to

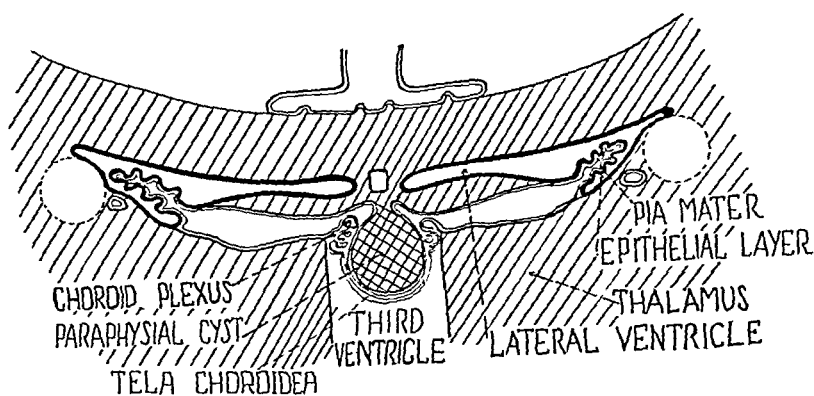


Fig. 4.—Adapted with modifications from Fig. 180 B of Larsell.<sup>21</sup> The formation of the primitive choroid plexuses is illustrated diagrammatically. A paraphysial cyst has been drawn in. It is shown sagging down upon the tela choroidea and, in turn, being enveloped by it. As the cyst enlarges and the pedicle thins, the choroid plexuses of the third ventricle will fuse at the pedicle. The cyst eventually is invested with the two layers of the tela choroidea which comprises the outer fibrovascular investment.

the erroneous conclusion by some writers that the cysts are derived from the choroid plexus. Although this pathogenetic conception is incorrect, these tumors are indeed intimately bound to the choroid plexus and tela choroidea. This raises surgical problems that will be more fully dealt with in later paragraphs. In time, if growth continues, the cyst enlarges until it occupies and fills the anterior portion of the third ventricle, eventually obstructing the intraventricular foramina. Since the tumors are exactly in the midline and are usually round, both foramina are likely to be blocked equally. The interference with drainage of the cerebrospinal fluid from the lateral ventricles into the third ventricle

102.6° F. but subsided gradually and became normal by the seventeenth postoperative day. At this time the ventricular and spinal fluid were xanthochromic. Indigo carmine dye instilled in the right lateral ventricle was promptly recovered from the left ventricle and appeared also in the spinal canal in a few minutes. The power of her left extremities rapidly improved during the postoperative period, vision was returning and she became alert and cheerful. She was up in a wheel chair on the eighteenth day and walking on the twentieth. She was discharged twenty-one days after operation. At this time there was no gross weakness of the left extremities although a Babinski sign was present. The left angle of her mouth drooped slightly. The ocular palsies had disappeared and the papilledema was subsiding. She was able to read newsprint easily. Mental examination showed only a moderate psychomotor retardation and an unwarranted jocularity.



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the position of the head. An explanation of this has been given in a previous paragraph. It must be pointed out, however, that the spectacular character of the phenomenon has made a greater impression than is warranted by the number of cases in which it has been seen. In those cases in which the patient came to operation, the sign was observed only in five instances (Table I) and in our case, which is included in the five, its existence became known only long after operation when the patient was pointedly questioned. Stookey found in an analysis of the literature that 39 per cent of patients had this symptom.<sup>3</sup> Nevertheless, it must be admitted that this sign, while suggestive, is not pathognomonic since it is occasionally observed with tumors of the fourth ventricle or those within the lateral ventricle. There have been three instances where the correct diagnosis was suspected or at least suggested and in none of these were postural headaches observed. More common but less dramatic has been the intermittency of the symptoms, periods of violent headache and vomiting appearing and vanishing with comfortable or entirely symptom-free intervals. This fact is perhaps of statistical value, but again surgeons of experience would hardly venture a diagnosis of tumor within the third ventricle on this ground alone, since intermittent headaches are so commonly experienced from tumors of various kinds in different locations.

Not only is a syndrome diagnostic of these tumors lacking, but a review of the literature reveals the somewhat astonishing fact that they may exist without producing evidence of intracranial hypertension although they cause other ominous symptoms. Slowly progressive dementia,<sup>17, 18</sup> a chronic convulsive state, primary optic atrophy, and other symptoms not ordinarily ascribed to intracranial pressure may comprise the clinical picture of paraphysial cysts.

Again, the histories of cases with paraphysial cysts show so many vagaries that little is obtained for diagnostic purposes from a study of the records. The first manifestations may announce themselves with apoplectiform rapidity, sudden coma and death terminating in a few hours what has apparently been a healthful life.<sup>18</sup> On the other hand, neurologic evidence for what appears to be diffuse degeneration of the nervous system may exist for years, symptoms of tumor being conspicuous by their absence. These considerations lead one to the view that diagnosis, with rare exceptions, depends upon evidence afforded by pneumography. Indeed, in operations which have been carried out for paraphysial cysts, pneumographic study has been relied upon as the final arbiter and in every instance has preceded surgery, the pre-pneumographic diagnosis usually having been unlocalized brain tumor.

The details of the pneumographic findings have been carefully described, first by Dandy<sup>1</sup> and later more fully by Davidoff and Dyke.<sup>5</sup> They vary somewhat, minor differences depending upon the completeness of the block of the intraventricular foramina, the integrity of the septum



ultimately results in a dilatation of the lateral ventricles which is generally symmetrical. Since, in some cases, the duration of symptoms has been short while necropsy or ventriculographic study has disclosed very large lateral ventricles, the conclusion seems inescapable that gradual dilatation of these chambers from an incomplete block may occur and yet cause no symptoms. The onset of violent headache, vomiting, and papilledema apparently occurs when the last bit of flow through the intraventricular foramina of one or both ventricles is completely obstructed. There is considerable reason to believe that impaction of the tumor into one or both foramina may occur for transient periods. Such episodes are marked by the sudden appearance of pronounced evidences of intracranial hypertension. The symptoms may subside even as abruptly. The explanation for this curious phenomenon is the fact that there is a certain degree of mobility to these pendulous tumors which hang from the roof of the third ventricle. A change in position of the head may dislodge the tumor enough to obstruct the intraventricular foramina suddenly and completely. Stookey thinks that yet another mechanism comes into play. The lesser veins of Galen are formed within the intraventricular foramina by the confluence of the veins of the choroid plexus and the veins draining the caudate nucleus and thalamus. Dislodgment of the tumor through alterations in position of the head, according to Stookey,<sup>3</sup> compresses the lesser veins of Galen at their origin causing venostatic edema of the basal ganglia as well as an increased secretion of cerebrospinal fluid due to the raised venous pressure in the choroid plexus. This latter phenomenon is thought to produce a vicious circle leading to a rapid and great increase of pressure within the lateral ventricles. Whatever the correct explanation may be, sudden death is not an uncommon ending to these episodes.

#### DIAGNOSIS

As McLean pointed out, the third ventricle being a cavity, tumors in it can have no distinctive symptomatology except those due to an obstructive hydrocephalus. Yet adventitious neurologic symptoms and signs may, and frequently do, appear from direct compression of neighboring neural structures. Direct injury of the hypothalamic nuclei in the floor and walls of the third ventricle may give rise to diabetes insipidus, obesity and genital dystrophy, and on several occasions has produced curious attacks characterized by flushing, lacrimation, sweating, and other evidences of a diffuse sympathetic discharge, the so-called diencephalic epilepsy of Penfield.<sup>16</sup> Focal paralyses and oculomotor disturbances have also been noted and many other neural disturbances for which the pathogenetic explanation is not clear. However, analysis of the numerous published protocols easily convinces one that no syndrome can be constructed which is typically produced by these tumors. While most neurologic writers subscribe to this view, some believe that a diagnostic symptom is the occurrence of violent headache with alteration in

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## DATA ON 17 CASES OF PARAPHYSIAL CYSTS

PNEUMOGRAPHIC DIAGNOSIS AND FINDINGS	METHOD OF OPERATIVE REMOVAL	POSTOPERATIVE COURSE AND RESULTS
Ventriculography; both lateral ventricles dilated and not communicating, no third ventricle visible	Right hemisphere retracted from falx; corpus callosum split and body of right lateral ventricle entered. Foramen of Monro identified and margin split anteriorly, tumor removed in toto	Stormy; temp. 102 to 104° F. for 17 days; light hemiplegia. Hemiparesis 10½ years later
Ventriculography; marked dilatation of both lateral ventricles which intercommunicated through ruptured septum; no third ventricle visible	Left hemisphere retracted from falx; posterior half of corpus callosum split and tela choroidea divided. Cyst aspirated and wall dissected free	Temp. 99 to 102° F. for 17 days; complete recovery
Ventriculography; air injected in one lateral ventricle showed dilatation but did not pass to other lateral ventricle. Some air seen in the third ventricle which outlined filling defect in the anterior portion	Horseshoe-shaped block of tissue resected from right frontal lobe and lateral ventricle entered; anterior margin of foramen of Monro split, cyst aspirated, and wall dissected free	Uneventful recovery
Ventriculography; huge dilatation of both lateral ventricles. No air visible in the third ventricle	Right occipital craniotomy and posterior portion of right hemisphere retracted from falx. Corpus callosum split and lateral ventricle entered; foramen identified and enlarged anteriorly, cyst contents aspirated, and wall dissected free.	Mental confusion and spatial disorientation for several weeks; abnormal temperature for 5 weeks. Well 6 months later except for mild mental disturbances
Ventriculography; both ventricles injected and huge dilatation observed. No third ventricle visible	Two-stage operation; first stage transcortical incision through right frontal lobe into lateral ventricle and tumor visualized. Second stage, ventricle re-entered, foramen of Monro enlarged posteriorly, tumor dissected free from choroid plexus	Fever 101° F. for one week, then uneventful recovery
Encephalography; lateral ventricles dilated. Air in the third ventricle outlining tumor in the anterior portion	First stage, right subtemporal decompression. Second stage, transcortical incision through right frontal lobe into lateral ventricle. Cyst extracted through dilated foramen of Monro	Visual impairment and disorientation for 4 weeks; complete recovery in 3 months
Ventriculography; both lateral ventricles greatly dilated. No third ventricle visualized	Transcortical incision through right frontal lobe into lateral ventricle; tumor seen filling dilated foramen of Monro, cyst contents aspirated, and wall dissected free	Uneventful and complete recovery except for poor vision
Ventriculography; dilated lateral ventricles communicating. Air in the third ventricle outlining a tumor in the anterior portion	Transcortical incision in right frontal lobe made through small horizontal dural slit. Lateral ventricle entered, foramen of Monro enlarged anteriorly, cyst contents cu-retted out, and wall dissected free	Uneventful and complete recovery

## SUMMARY OF CLINICAL, DIAGNOSTIC, AND OPER.

AUTHORS AND SURGEONS	AGE AND SEX	DURATION OF SYMPTOMS	CLINICAL HISTORY	NEUROLOGIC FINDINGS
W. E. Dandy Case 1 1933	24 F	9 Mo.	Severe and continuous headaches	Bilateral papilledema of 6 diopters; weakness of sixth nerve
W. E. Dandy Case 2 1933	34 F	10 Yr.	Recurrent bouts of headache and vomiting; fainting spells; disturbances in equilibrium, diplopia, and failing memory	Mentally dull; bilateral papilledema; slight bilateral exophthalmos; suggestive Romberg sign
W. E. Dandy Case 3 1933	10 F	8 Mo.	Repeated bouts of headache; one tonic convulsion; diplopia and strabismus	Enlarged head; bilateral papilledema, strabismus; diagnosis of intraventricular tumor made on basis of periodic attacks
W. E. Dandy Case 5 1933	37 F	5 Yr.	Repeated bouts of severe headache, dizziness and vomiting precipitated by change in position of head; occasional loss of consciousness in attacks and bradycardia as low as 44 per minute in attacks	Neurologic examination negative, fundi normal, ventriculography performed because of history
H. M. Zimmerman, and W. J. German Case 1, 1933 (Operation by Sam Harvey)	26 M	4 Yr.	Recurrent attacks of headache, weakness and drowsiness of increasing severity and frequency; two episodes of unconsciousness; sweating and flushing attacks; blurring of vision	Bilateral papilledema of 6 diopters; clinical impression of tumor of third ventricle
Byron Stookey Case 2 1934	43 M	7 Mo.	Severe bitemporal headache, blurring of vision, tinnitus	Bilateral papilledema of 2 3 diopters
Byron Stookey Case 3 1934	31 M	1 Yr.	Onset with spells of dizziness and weakness; later continuous headaches and drowsiness, polydipsia and polyuria, exophthalmos; one fainting spell	Bilateral papilledema and bilateral exophthalmos; obesity and hirsutism
C. B. Mason Case 2 1934	23 F	5 Yr. (?)	One week severe headaches followed by 5-year symptom-free interval; one month before admission developed severe headaches and series of convulsions, vomiting attacks and failing vision	Bilateral papilledema, reduced vision, inferior nasal defect in field of right eye; clinical impression, tumor of third ventricle or bifrontal tumor

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## DATA ON 17 CASES OF PARAPHYSIAL CYSTS

PNEUMOGRAPHIC DIAGNOSIS AND FINDINGS	METHOD OF OPERATIVE REMOVAL	POSTOPERATIVE COURSE AND RESULTS
Ventriculography; both lateral ventricles dilated and not communicating, no third ventricle visible	Right hemisphere retracted from falx; corpus callosum split and body of right lateral ventricle entered. Foramen of Monro identified and margin split anteriorly, tumor removed in toto	Stormy; temp. 102 to 104° F. for 17 days; light hemiplegia. Hemiparesis 10½ years later
Ventriculography; marked dilatation of both lateral ventricles which intercommunicated through ruptured septum; no third ventricle visible	Left hemisphere retracted from falx; posterior half of corpus callosum split and tela choroidea divided. Cyst aspirated and wall dissected free	Temp. 99 to 102° F. for 17 days; complete recovery
Ventriculography; air injected in one lateral ventricle showed dilatation but did not pass to other lateral ventricle. Some air seen in the third ventricle which outlined filling defect in the anterior portion	Horseshoe-shaped block of tissue resected from right frontal lobe and lateral ventricle entered; anterior margin of foramen of Monro split, cyst aspirated, and wall dissected free	Uneventful recovery
Ventriculography; huge dilatation of both lateral ventricles. No air visible in the third ventricle	Right occipital craniotomy and posterior portion of right hemisphere retracted from falx. Corpus callosum split and lateral ventricle entered; foramen identified and enlarged anteriorly, cyst contents aspirated, and wall dissected free.	Mental confusion and spatial disorientation for several weeks; abnormal temperature for 5 weeks. Well 6 months later except for mild mental disturbances
Ventriculography; both ventricles injected and huge dilatation observed. No third ventricle visible	Two stage operation; first stage transcortical incision through right frontal lobe into lateral ventricle and tumor visualized. Second stage, ventricle re-entered, foramen of Monro enlarged posteriorly, tumor dissected free from choroid plexus	Fever 101° F. for one week, then uneventful recovery
Encephalography; lateral ventricles dilated. Air in the third ventricle outlining tumor in the anterior portion	First stage, right subtemporal decompression. Second stage, transcortical incision through right frontal lobe into lateral ventricle. Cyst extracted through dilated foramen of Monro	Visual impairment and disorientation for 4 weeks; complete recovery in 3 months
Ventriculography; both lateral ventricles greatly dilated. No third ventricle visualized	Transcortical incision through right frontal lobe into lateral ventricle; tumor seen filling dilated foramen of Monro, cyst contents aspirated, and wall dissected free	Uneventful and complete recovery except for poor vision
Ventriculography; dilated lateral ventricles communicating. Air in the third ventricle outlining a tumor in the anterior portion	Transcortical incision in right frontal lobe made through small horizontal dural slit. Lateral ventricle entered, foramen of Monro enlarged anteriorly, cyst contents cu-retted out, and wall dissected free	Uneventful and complete recovery

AUTHORS AND SURGEONS	AGE AND SEX	DURATION OF SYMPTOMS	CLINICAL HISTORY	NEUROLOGIC FINDINGS
L. M. Davidoff, and C. Dyke Case 4 1935	19 M	10 Mo.	Severe headaches induced by flexion of neck; headaches progressively more severe, flashes before eyes, one fainting spell	Bilateral papilledema
L. M. Davidoff, and C. Dyke Case 5 1935	27 F	6 Yr.	Early complaints of mild intermittent headaches, transient blurring of vision and one convulsion; later severe headaches induced by change of posture	Bilateral papilledema
L. M. Davidoff, and C. Dyke Case 7 1935	27 F	2 Mo.	Sudden onset of severe continuous temporal and frontal headaches	Bilateral papilledema
J. F. Paterson, and M. Leslie 1935	34 M	2½ Yr.	Recurrent attacks of headaches becoming more severe and accompanied by dizziness, vomiting and unconsciousness; progressive visual failure	Bilateral papilledema; half reduced
A. J. McLean Case 2 1936	16 F	4 Mo.	Amblyopia on change of posture; recurrent attacks of headache and vomiting induced and relieved by change in posture; diplopia	Bilateral papilledema, weakness of right external rectus, central facial weakness, tagmus, unsteadiness on dysmetria and ataxia arms; clinical impression of chronic arachnoiditis
W. J. Gardner, and O. Turner 1937	31 F	10 Mo.	Severe frontal headaches and attacks of head pain; failing vision	Bilateral papilledema; spinal pressure, 250-300 of water
M. A. Shaver Case 1, 1940 (Surgeon W. S. Keith)	26 F	2 Yr.	Recurrent attacks of headache and vomiting becoming progressively more severe	Bilateral papilledema
M. A. Shaver Case 2, 1940 (Surgeon, K. G. McKensie)	28 F	5 Mo.	Progressive visual failure	Bilateral papilledema
L. M. Weinberger, and B. Boshes 1942	22 F	3 Wk.	Sudden onset of severe continuous headaches associated with vomiting attacks; headaches aggravated by supine position, relieved by erect posture; diplopia	Bilateral papilledema of 6+; bilateral external rectus palsies; clinical impression of unlocalizable brain tumor

PNEUMOGRAPHIC DIAGNOSIS AND FINDINGS	METHOD OF OPERATIVE REMOVAL	POSTOPERATIVE COURSE AND RESULTS
Encephalography, symmetrical dilatation of lateral ventricles. Air in the third ventricle outlining a tumor in the anterior portion	Transcortical incision through right frontal lobe into lateral ventricle. Tumor seen in dilated foramen of Monro. Cyst aspirated and wall dissected free	Moderate fever 3 weeks and then complete recovery
Ventriculography, both lateral ventricles dilated. No third ventricle visible and air shadows in foramina of Monro sharply cut off. Shadow of tumor seen between lateral ventricles	Transcortical incision through right frontal lobe into lateral ventricle. Tumor seen in dilated foramen of Monro. Cyst contents evacuated and wall dissected free	Fever for several weeks, recovery. Status(?)
Encephalography, lateral ventricles dilated. Air in third ventricle outlining tumor in anterior portion	Transcortical incision through right frontal lobe into lateral ventricle. Cystic tumor projected through dilated foramen of Monro, cyst contents removed, and wall dissected free	Stuporous and hemiplegic for several days, moderate hemiparesis and mental confusion 6 weeks later
Ventriculography, marked dilatation of both lateral ventricles. No third ventricle visible. Indigo carmine dye passed readily from one lateral ventricle to other through ruptured septum lucidum	Block of right frontal lobe resected and ventricle entered. Tumor seen in dilated foramen which was enlarged anteriorly, tumor removed in toto	Fever for 6 days up to 102.4° F., mental confusion for 2 weeks. Two convulsions in postoperative period and complete recovery in 8 months
Ventriculography, one lateral ventricle was injected and appeared markedly dilated. Air did not cross to other lateral ventricle but a small amount was seen in the third ventricle which outlined filling defect in anterior portion	Wedge shaped block of tissue resected from left frontal lobe and lateral ventricle entered. Tumor blocked foramen of Monro. Cyst evacuated and wall dissected free, moderate hemorrhage	High fever for 5 weeks, bloody CFS, coarse tremors, complete recovery in 8 months except for slight aphasia
Ventriculoencephalography, dilated lateral ventricles. Posterior portion of the third ventricle visualized with air outlining tumor in anterior portion. Indigo carmine dye passed from one lateral ventricle to other	Transcortical incision through right frontal lobe into lateral ventricle. Tumor presented in foramen of Monro which was enlarged anteriorly. Cyst evacuated and capsule dissected free	Uneventful and complete recovery
Ventriculography, large dilated lateral ventricles. No third ventricle visualized	Transcortical incision through right frontal lobe into lateral ventricle. Tumor presented in foramen of Monro which was enlarged anteriorly, cyst evacuated and capsule dissected free	Uneventful and complete recovery except for epilepsy controlled by barbiturates
Ventriculography, one lateral ventricle injected with air and appeared dilated. No air visualized in other lateral ventricle or in third ventricle	Transcortical incision through right frontal lobe into lateral ventricle, cyst presented in foramen of Monro which was enlarged anterosuperiorly. Cyst removed in toto	Slight fever, complete recovery
Ventriculography, air injected into both lateral ventricles, both ventricles dilated, third ventricle not visualized. Indigo carmine dye injected into one lateral ventricle did not pass to other	Transcortical incision through right frontal lobe into lateral ventricle. Cyst grasped by instrument inserted into third ventricle and withdrawn through foramen of Monro	Moderate fever for 2 weeks, intraventricular hemorrhage, weakness of left extremities, complete recovery in 3 months

AUTHORS AND SURGEONS	AGE AND SEX	DURATION OF SYMPTOMS	CLINICAL HISTORY	NEUROLOGIC FINDINGS
L. M. Davidoff, and C. Dyke Case 4 1935	19 M	10 Mo	Severe headaches induced by flexion of neck; headaches progressively more severe, flashes before eyes, one fainting spell	Bilateral papilledema
L. M. Davidoff, and C. Dyke Case 5 1935	27 F	6 Yr.	Early complaints of mild intermittent headaches, transient blurring of vision and one convulsion, later severe headaches induced by change of posture	Bilateral papilledema
L. M. Davidoff, and C. Dyke Case 7 1935	27 F	2 Mo	Sudden onset of severe continuous temporal and frontal headaches	Bilateral papilledema
J. F. Paterson, and M. Leslie 1935	34 M	2½ Yr	Recurrent attacks of headaches becoming more severe and accompanied by dizziness, vomiting and unconsciousness; progressive visual failure	Bilateral papilledema, v half reduced
A. J. McLean Case 2 1936	16 F	4 Mo	Amblyopia on change of posture, recurrent attacks of headache and vomiting induced and relieved by change in posture, diplopia	Bilateral papilledema, weakness of right external rectus, central facial weakness, tagmus, unsteadiness of gait, dysmetria and ataxia arms, clinical impression of chronic meningoencephalitis
W. J. Gardner, and O. Turner 1937	31 F	10 Mo	Severe frontal headaches and attacks of head pain; failing vision	Bilateral papilledema; increased spinal pressure, 250-300 mm. of water
M. A. Shaver Case 1, 1940 (Surgeon W. S. Keith)	26 F	2 Yr	Recurrent attacks of headache and vomiting becoming progressively more severe	Bilateral papilledema
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L. M. Weinberger, and B. Bosches 1942	22 F	3 Wk.	Sudden onset of severe continuous headaches associated with vomiting attacks, headaches aggravated by supine position, relieved by erect posture; diplopia	Bilateral papilledema of 6 dieters; bilateral external rectus palsies, clinical impression of unlocalizable brain tumor

by repeated ventricular punctures during the forty-eight hours that intervened between diagnosis and operation.

Due to the infrequency of paraphysial cysts, methods of operation have varied considerably in regard both to the anatomic approach and the details of surgical technique. Dandy, in his early experiences, used three different methods of attacking these tumors. In his first case he retracted the right hemisphere from the falx in the parietal region, split the corpus callosum and entered into the right lateral ventricle. Working within the lateral ventricle, he removed the tumor through the foramen of Monro. In his second case, he retracted the right hemisphere from the falx, split the corpus callosum and tela choroidea, and entered directly into the third ventricle thus exposing and subsequently removing the tumor. In his third case, he resected a large block of tissue from the right frontal lobe and entered the lateral ventricle opposite to the foramen of Monro and removed the tumor through the foramen. It is our impression, gained from his subsequent writings,<sup>20</sup> that he favors the last method. All other operators who have succeeded in removing paraphysial cysts have adopted the transcortical method of entering the lateral ventricle. This seems to carry less hazards than the transcollosal route for several reasons. It avoids retraction of the hemisphere and ligation of the veins entering the longitudinal sinus, maneuvers which are likely to cause swelling of the hemisphere. It avoids dealing with the veins of Galen. Lastly, by offering a direct route to the foramen of Monro, the exposure is more ample, hemorrhage can be more easily dealt with, and there is less possibility of injuring vital neural structures.

Dandy,<sup>1</sup> Paterson and Leslie,<sup>6</sup> and McLean<sup>7</sup> have resected round or wedge-shaped blocks of tissue from the frontal lobe in order to gain access to the lateral ventricle but this seems to be an unnecessary sacrifice of brain substance and offers slight or no advantage over a simple linear transcortical incision. The incision should be made well anterior to the motor cortex and preferably at right angles to it. The advantage of a horizontally placed incision is that the pressure and contusing effects of retraction are not exerted against the motor cortex as they are if the incision is made in a vertical (dorsoventral) direction. This precaution makes it easier to avoid a postoperative hemiplegia. In our own case, there was a moderate weakness of the left extremities for several days and in some cases the weakness has been marked and persistent.

Since paraphysial cysts lie exactly in the midline, there is no occasion ever to approach the tumor from the left side. Where this has been done by McLean and by Dandy, aphasic disturbances or defects in spatial orientation have followed.

It is our impression that operation for a paraphysial cyst should be performed in one stage. While Harvey<sup>2</sup> and Stookey<sup>3</sup> succeeded in accomplishing two-stage removals, there have been two other cases where death has occurred between the first and second stage.<sup>2, 3</sup> Operative trauma with its attendant cerebral swelling and disturbance of the intracranial



lucidum, the type of air study (ventriculography or encephalography), and whether one or both ventricles are punctured in the performance of ventriculography.

Although Davidoff and Dyke<sup>5</sup> and Stookey<sup>3</sup> performed encephalography in three cases and succeeded in diagnosing the tumors, it is the opinion of most neurosurgeons that the presence of intracranial hypertension makes this procedure hazardous, especially so in the light of recent knowledge respecting the mechanism of tentorial herniation. Their encephalographic findings, however, are summarized in Table I.

If bilateral burr holes are made and both lateral ventricles cannulated, a characteristic ventriculogram is obtained. Both lateral ventricles appear dilated, and occasionally enormously so; they are usually symmetrical. No air is visualized within the third ventricle in any position of the head. The foramina of Monro are dilated but the air shadows are sharply cut off (Fig. 1). Occasionally, in the anteroposterior projections, the convex outlines of the tumor may be seen bulging into one or both lateral ventricles. Rarely, the block of the intraventricular foramina may not be complete so that a little air enters the third ventricle and outlines the tumor.

If only one lateral ventricle is cannulated and the septum lucidum is intact, no air will escape from the ventricle and the roentgen film will show a single dilated lateral ventricle. On the other hand, if the septum lucidum is frayed and torn, as is frequently the case, air will pass through it and both ventricles will be visualized. With either of these two circumstances, interpretation may be confusing since the question of a technical fault may arise. The suspicion may occur that the absence of air in the third ventricle is due to inadequate drainage of the ventricular system or to inadequate diffusion of air throughout the system. For these reasons it seems that less difficulty in roentgen interpretation will be encountered if both ventricles are injected with air at the same time.

Preliminary to air injection, it is common practice to instill a few cubic centimeters of indigo-carmin dye into one lateral ventricle and then attempt to recover it from the other; failure to do so indicates a block of the intraventricular foramina, while passage of the dye is generally taken to indicate free communication. It may be misleading to rely upon the passage of dye, as several observers have pointed out<sup>6</sup> that dye may pass through, owing to rupture of the septum lucidum or to an incomplete block of the foramina of Monro although a large tumor may be present.

#### OPERATIVE TECHNIQUE

Operation should be undertaken when the ventriculographic diagnosis is made. It seems that disaster is particularly prone to occur after ventriculography, with third ventricle tumors, if the patients are not operated upon promptly. In our own case a fatality was avoided only

by repeated ventricular punctures during the forty-eight hours that intervened between diagnosis and operation.

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#### OPERATIVE TECHNIQUE

Operation should be undertaken when the ventriculographic diagnosis is made. It seems that disaster is particularly prone to occur after ventriculography, with third ventricle tumors, if the patients are not operated upon promptly. In our own case a fatality was avoided only

struct the cerebral aqueduct. The patient in Dandy's<sup>1</sup> fifth case died after a stormy postoperative course from obstruction of the aqueduct.

If the patients survive the operative procedure and the immediate postoperative course, complete recovery is generally to be expected. From this point of view, paraphysial cysts are extremely favorable tumors. Of the 17 cases operated upon, 13 showed complete or almost complete recovery, 2 had residual hemiparesis, 1 had a mild residual aphasia, and 1 was neurologically normal but had epilepsy which was controlled with barbiturates. One of the cases of hemiparesis was reported only six weeks after operation<sup>7</sup> and further recovery very likely took place.

If the incision through the cortex is placed well anterior to the motor strip, complete recovery should follow operation, since removal of the tumor ordinarily entails no trauma to vital structures and normal ventricular drainage is promptly established. Focal epilepsy should be an uncommon sequel as little glial scar forms when the incision is carried down to the ventricle.

In only one case has a postoperative pneumogram been performed, but in this instance the ventricular system was entirely patent.

#### SUMMARY

An additional case is recorded of a successful removal of a paraphysial cyst, thus bringing the number of reported surgical recoveries to seventeen. In an effort to standardize the surgical management of these tumors, the literature is reviewed and certain conclusions reached concerning the most favorable methods and the techniques to be employed in both diagnosis and operation.

#### Addendum

Fourteen months after operation, the patient writes that she is entirely well and is working full time. There have been two brief attacks consisting of twitching of the left side of the face but with no loss of consciousness.

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hydrodynamics seems to carry a much greater hazard if the tumor is not removed and the ventricular block released. For this reason, unless the desperate condition of the patient does not permit, all efforts should be made to remove the tumor at one sitting. This also applies to those rare instances in which the lateral ventricles are not sufficiently dilated for surgical maneuvers to be carried out easily within the ventricle. A preliminary subtemporal decompression to allow enlargement of the ventricle with the period of necessary waiting may be more dangerous than attempting to work within a small ventricle.

The experience of surgeons who have successfully removed paraphysial cysts shows that ample working room is obtained within the dilated lateral ventricle. The structures are seen clearly with the aid of illuminated retractors which may be easily introduced within the ventricle. The foramen of Monro may be found promptly by following the choroid plexus forward until it is seen to disappear. The cyst, if large, presents itself as a greenish or bluish mass in a dilated foramen, and this is the usual finding. If small, it may not be visible and the foramen may appear as a small slit. By tugging gently on the choroid plexus, the cyst wall can be brought into view in the aperture of the foramen and then grasped with an instrument. In our case, it was possible thus to tease the cyst through the foramen, but if the tumor is quite large, one must resort to other methods of delivery.

Some operators have first evacuated the thick colloidal contents of the cyst by aspiration and then delivered the capsule through the foramen. Others have enlarged the foramen by slitting its margin. The slit can be made safely only in the anterior rim of the foramen which is formed by the descending pillars of the fornix. Several small veins lie in this region, the largest of which is the vein of the septum lucidum. These may be coagulated easily and the enlarging of the foramen becomes a bloodless procedure.

As pointed out earlier, the paraphysial cyst is intimately connected to the choroid plexus and the tela choroidea, but this is its only point of attachment. When the cyst or the cyst wall is in full view this attachment can be readily clipped or coagulated and the cyst cut free. This is a simple but important step, for should the cyst be inadvertently torn away, severe hemorrhage, difficult to control, will result and the floor of the third ventricle be injured in the attempt to handle the bleeding.

Since the manipulations around the foramen may produce edema and thus obstruct drainage of the ventricle for a few days, it is worth while taking the precaution of tearing a small opening in the septum lucidum, if one is not already present. The occurrence of cerebral swelling as a consequence of operative manipulations may require drainage of the ventricle for a few days with a Penrose drain or an indwelling cannula. Drainage also serves to remove blood and detritus from the ventricle which, if not removed, may not only cause fever but conceivably may ob-

## THE USE OF DETERGENTS IN THE CLEANSING AND LOCAL TREATMENT OF BURNS

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IN CIVIL life, the most common causes of burns are (1) fire, (2) hot liquids, (3) contacts with hot surfaces, (4) electric burns, (5) chemical burns, and (6) sunburn.<sup>1</sup> The common contaminants of such injuries are the various forms of particulate soil and the charred remnants of clothing. Fuel oil and grease are sometimes found on burned surfaces following automobile and the occasional maritime accidents. The usual reason for the presence of oil-, fat-, or grease-covered burns in civilian practice is the application of these substances to the burned area either by the patient or someone rendering first aid.<sup>1</sup>

In time of war, however, different types of burns result. They are more frequent and severe and occur under conditions which may render emergency treatment difficult. War burns are most often due to (1) gun or bomb flash, (2) boiling or burning oil, especially in disasters at sea, (3) incendiary bombs, (4) gasoline explosions, (5) electricity, and (6) chemicals (mustard gas, phosphorus, etc.).<sup>2</sup> Besides the delay which is often incurred before proper treatment can be instituted, these burns are usually contaminated by particulate soil, charred clothing, and often by heavy coats of grease and hydrocarbon oils. There may be other injuries in addition.

The difficulties encountered in cleansing and débridement are obvious, and the inadequacies of most cleansing methods used at present have been admitted by workers in the field. This is especially true in burns contaminated by greases and oils. Indeed in certain such cases subsequent tanning procedures have proved to be inefficient or have had to be omitted.<sup>3</sup> The literature, both before and during the present world conflict, abounds in references emphasizing the lack of a cleansing method which would not subject the already shocked patient to general anesthesia and in which vigorous scrubbing with soaps and irritating solvents would not be necessary. These latter methods often injure or remove healthy tissue.<sup>4, 5</sup>

The coagulation treatment of burns appears to be efficient and in many cases practical.<sup>6</sup> The eschar, when formed on a relatively clean surface by tannic acid, gentian violet, triple dye, or the like, accomplishes many purposes: (1) it prevents the loss of fluid, electrolytes, and protein from the burned surface; (2) it is an efficient barrier against exogenous infection, especially dangerous in the critical, early period

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The coagulation treatment of burns appears to be efficient and in many cases practical.<sup>6</sup> The eschar, when formed on a relatively clean surface by tannic acid, gentian violet, triple dye, or the like, accomplishes many purposes: (1) it prevents the loss of fluid, electrolytes, and protein from the burned surface; (2) it is an efficient barrier against exogenous infection, especially dangerous in the critical, early period

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TABLE I

ANALYSIS OF PRELIMINARY CLEANSING METHODS EMPLOYED IN THE TREATMENT OF BURNS

CLEANSING METHOD	SEDATION	TREATMENT TO FOLLOW	REMARKS
Slight superficial cleansing	Morphine	Saline baths and dressings	Bulky; much nursing needed; only a few patients can be treated; danger of infection
Slight superficial cleansing	Morphine	Triethanolamine*-sulfadiazine spray <sup>21</sup>	Potentially infected material left behind; sulfadiazine not all-powerful
Moderate, gentle scrubbing and débridement (white soap and water)	Morphine	Vaseline gauze and pressure dressings <sup>22</sup> Tanning or coagulation <sup>23, 24</sup>	No effective removal of layers of grease or oil
Moderate to considerable scrubbing with saline or green soap and water Ether soaps, grease solvents Moderate to considerable débridement	Morphine, general anesthesia	Tanning or coagulation <sup>5, 26</sup>	Shock increased by scrubbing and anesthesia; healthy tissue injured or removed by solvents and scrubbing methods

\*Triethanolamine has detergent properties but is employed in the above mixture for its penetrant and solvent qualities.

of treatment; (3) it further decreases the incidence of shock by rapidly diminishing pain; and (4) it allows for greater ease in nursing and in transportation. Other methods offer no such advantages. Saline baths are efficacious when adequate nursing and hospital facilities are available but are not practical in widespread disasters.<sup>4</sup>

Infection is the great complication in the coagulation treatment and, indeed, in any proscribed treatment for burns. The probable origin of most suppuration occurring under "tans" is the initial contamination which had never been fully eradicated.<sup>4</sup> Certain infections may have their portal of entry at the edges of the eschar or in cracks in its surface.

More recently, in preference to coagulation procedures, immobilization by pressure dressings has been suggested as a more effective treatment than tanning.<sup>22</sup>

In the past few years, a group of chemical compounds, the so-called synthetic detergents, have gained wide use, at first in industry and more recently in dermatology. Detergents are substances in which the cleansing properties are dependent on a bipolarity of chemical structure. Most of these substances show a hydrophilic, or water-attracting, group and a hydrophobic group which finds its greatest attraction toward solids and liquids not easily wet by water (that is, certain particulate soil, oils, and greases).

Many types of agents present these necessary chemical groups in their molecular structure. They are listed in Table II.

TABLE II  
A LIST OF THE MAIN TYPES OF DETERGENT MOLECULES\*

1. Sulfonated vegetable or animal oils
2. Sulfated alcohols
3. Sulfonated fatty esters or amides
4. Sulfonated alkylated aromatic hydrocarbons
5. Sulfonated ethers
6. Sulfonated aliphatic di-esters
7. Phosphated or borated fatty alcohols
8. Sulfonated hydrocarbons
9. Fatty amine salts

\*After Lane and Blank.<sup>7</sup>

The mechanism of action becomes apparent when a substance with such remarkable bipolarity is mechanically distributed throughout a water-insoluble medium, either particulate or homogeneous. The hydrophobic pole will orient and fix itself about the particle or molecule of

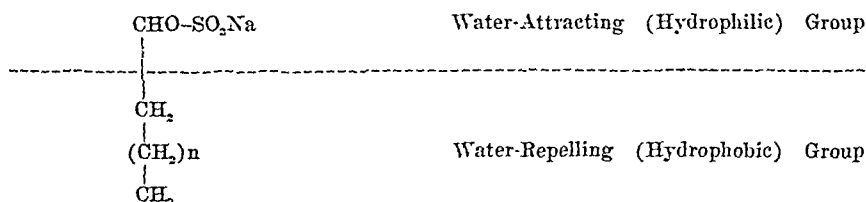


Fig. 1.—The diagrammatic configuration of a simple synthetic detergent.

homogeneous substance (oil), leaving its hydrophilic, or water-attracting, pole projecting outward in radial fashion (Fig. 2). A particle or molecule thus coated has an external layer of a water-soluble or a water-attracting group which renders the particle "solubilized," or more easily influenced by water.

Because the hydrophobic pole of the detergent is attracted to water-repelling substances, these agents are endowed with a variable amount of penetrating power, due to the attempt of this attraction to satisfy itself. The amount of mechanical agitation necessary to distribute uniformly a detergent through a layer of grease so that the entire grease layer may be subsequently washed off with water depends on the penetrating power of the particular detergent or detergent mixture employed.

Synthetic detergents are particularly fitted for the cleansing and débridement of those burns contaminated with and covered by a layer of grease, oil, and particulate matter. Most of them are nonirritating and have a pH which varies from neutrality to moderate alkalinity. Many have been used repeatedly and for long periods as soap substitutes for sensitive skins and as ingredients in dermatologic ointments.<sup>7, 8, 9, 10</sup> Nearly all of them have bacteriostatic and some bactericidal power, especially for the cocci found on the skin,<sup>11, 12, 14, 15, 16</sup> and many have proved

noninjurious to animals, even after prolonged oral and parenteral administration.<sup>17</sup> As an antiseptic, the application of some of the synthetic detergents to wounds and even to empyema cavities has already been tried either alone or with other antibacterial agents.<sup>11, 12, 14, 25</sup> One could hardly desire a more compatible array of qualities.

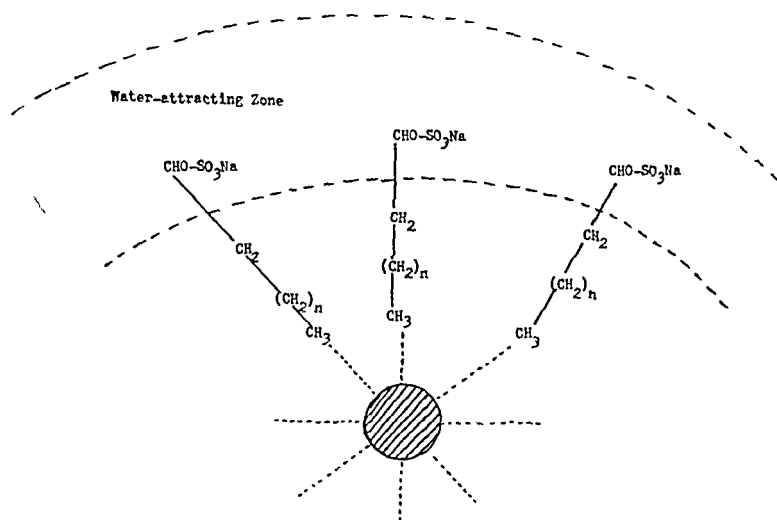


Fig. 2.—The hydrophobic poles of the detergent molecules coat and are adsorbed at the surface of the nonwetting, water-repelling particle or molecule. The hydrophilic poles project away from the particle to form a halo of water-attracting groups, thus "solubilizing" the particle of soil or molecule of grease.

Nearly 100 tests, each employing a different single detergent or detergent mixture, have been made on the normal, intact human skin. These experiments were all of a similar nature. Their purpose was to determine the effectiveness of the agent or mixture tested in removing from a given surface a layer of grease, oil, or fat, often purposely contaminated with particulate matter. The time and mechanical force necessary to disperse the agent throughout the grease or oil was also estimated and considered in the evaluation. Some six different mixtures proved most effective and required the least mechanical dispersion before the layer of grease was thoroughly and uniformly mixed with the agents used. With all of the effective mixtures, running water would then, within a few seconds, wash off the grease-detergent or oil-detergent combination. A clean skin remained, which, when dried by blotting, presented a definitely nongreasy feel, drier even than untreated normal skin. In other words, not only had the applied grease or oil been effectively removed, but along with it the natural skin oils, leaving a surface ready for the application of dye or water-soluble tanning agent. No signs or symptoms of skin irritation resulted except dryness, which occurred after repeated use. All of the mixtures listed in Table III in comparative tests proved to be cleansing agents far superior to green soap and water.

Since the cleansing of a given burned area is carried out only once, more powerful detergent combinations and stronger concentrations may be employed than would be considered suitable for repeated use (such as a soap substitute). Also, as a careful study of Table III reveals, it has been possible to employ adjuvant penetrant agents in some mixtures to lessen the amount of mechanical dispersing force necessary to distribute the detergent throughout the grease layer. No irritation resulted from the application of these penetrating agents to small skin areas or to relatively small burned areas in clinical cases.

The composition of certain detergent mixtures was based upon the following theoretical concept which subsequently proved to be efficacious in actual practice. For a long time it has been known that oils are detergents in a sense, and it has been found that grease and heavy oils may be removed from the skin by rubbing a readily mixing fat or oil into the grease layer and then washing with soap and water.<sup>18</sup> It is known, therefore, that hydrocarbon oils are miscible with grease and hence easily penetrate grease and oil layers with the aid of some mechanical dispersion. If one then subjects these hydrocarbon oils to the action of concentrated sulfuric acid, one or more sulfonate groups, which are water soluble, are chemically added to the molecule, forming a sulfonated oil or petroleum. This molecule, which possesses an oil-soluble pole and a water-soluble pole, fulfills the basic requirements previously described for a typical detergent. At the same time, it preserves in its only slightly but significantly altered molecule the power to penetrate other grease or oil hydrocarbon layers. Thus, sulfonated petroleum (Sulfate, Glyco) is used in most of the above mixtures, not only because of its own penetrating and detergent powers, but also as a vehicle or carrier for more powerful detergent substances. These latter otherwise might not be able to penetrate a grease layer except after considerable mechanical assistance in the form of massage. Again, once the detergents have been uniformly dispersed throughout the grease or oil, running water will wash both grease and detergent away. There is usually more attraction between detergent and the hydrophobic grease or particulate soil, so that the molecule of soil is literally dragged along with the attached detergent as the latter is carried away by the stream of water.<sup>19</sup>

For civilian use, in those burns contaminated only by light oils, ointments, or fats, usually applied by someone rendering first aid, almost any detergent mixture will prove efficient.

In military practice, however, burns are often covered with heavy fuel oil or grease, requiring more powerful cleansing mixtures which are easily dispersed throughout a heavy layer of these contaminating substances. While in burns sustained on land, fresh water is usually available to wash off oil-detergent combinations, in disasters at sea, salt water is the only water to be had in quantity. Detergent mixtures designed for the cleansing of burns on board ship must therefore possess

noninjurious to animals, even after prolonged oral and parenteral administration.<sup>17</sup> As an antiseptic, the application of some of the synthetic detergents to wounds and even to empyema cavities has already been tried either alone or with other antibacterial agents.<sup>11, 12, 14, 25</sup> One could hardly desire a more compatible array of qualities.

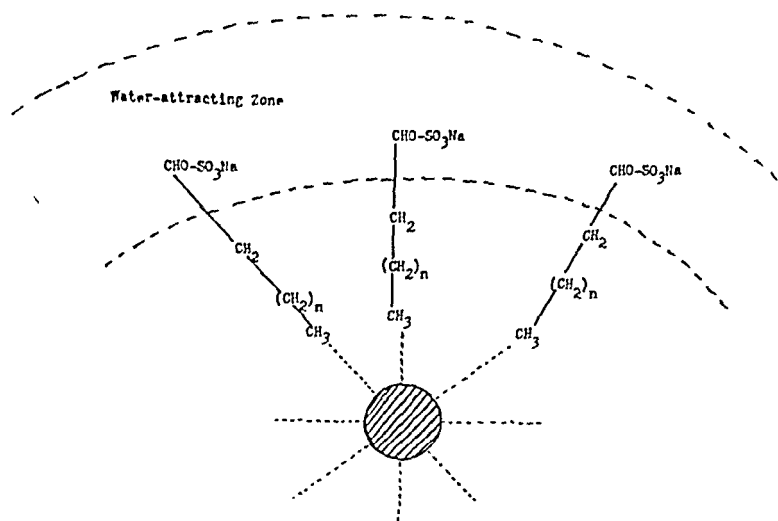


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TABLE III  
THE MOST EFFICIENT OF 100 DETERGENTS AND DETERGENT MIXTURES TESTED \*

COMMERCIAL NAME	PROPORTIONS USED	CHEMICAL NATURE	ACTION	PHYSICAL NATURE OF MIXTURE
Sulfatate				
Atlas-G 772 S (Atlas Powder Co.)	9 parts 1 part	Sulfonated petroleum Sorbitan laurate	Penetrant and detergent Emulsifier	Clear orange-yellow oil Soluble in 3% NaCl
Sulfatate (Glyco Products Co.)	11 parts	Sulfonated petroleum	Penetrant and detergent	Clear, orange-yellow oil
Aerosol OT 25% aq. (Am. Cyanamid Co.)	1 part	Di-octyl sodium sulfosuccinate	Detergent	Soluble in 3% NaCl
Sulfatate				
Orvus (Procter & Gamble Co.)	19 parts 1 part	Sulfonated petroleum A fatty alcohol sulfate	Penetrant and detergent Detergent	Clear, orange-yellow oil Soluble in 3% NaCl
Sulfatate	49 parts	Sulfonated petroleum	Penetrant and detergent	Clear, yellow oil
Tergitol-4 (Carbon & Carbide Co.)	1 part	Higher secondary alkyl sodium sulfonate	Detergent	Soluble in 3% NaCl
Sulfatate				
Oil Turkey Red (Eimer & Amend)	6 parts 5 parts	Sulfonated petroleum Sulfonated castor oil	Penetrant and detergent Penetrant and detergent	Clear, orange-yellow oil Soluble in 3% NaCl
Aerosol OT 25% aq.	1 part	Di-octyl sodium sulfosuccinate	Detergent	
Oil Turkey Red	11 parts	Sulfonated petroleum	Penetrant and detergent	Thick, orange-yellow oil
Aerosol OT 25% aq.	1 part	Di-octyl sodium sulfosuccinate	Detergent	Soluble in 3% NaCl

\*In all tests made on normal, intact skin, No. 6 fuel oil and also a very heavy grease (Permatex Water Pump Lubricant S-W, Permatex Co., Sheepshead Bay, N. Y.) were the final test substances.

the additional quality of solubility in sea water. Mixtures of various types are included in Table III. They all embody principles already discussed. Many other similarly patterned detergent mixtures are of course possible and are being investigated at this writing.

As outlined, the cleansing of a grease- or oil-covered burn is thus rendered as simple as possible. Penetration of the oily layer and union of detergent and oil molecules constitute the first step, and the non-traumatic washing away of grease and other superficial soil completes the cleansing procedure.

#### CLINICAL APPLICATION

Twenty-five patients with burns were treated in the Reception Ward of the Mount Sinai Hospital, New York City. All of these patients, who were ambulatory, sustained burns which were second degree in nature and involved a relatively small area of skin. In most instances, the burned areas, when first seen, were covered with ointments, fats, or oils, although an occasional area was contaminated with lubricating grease and considerable particulate matter. Several electrical burns of a superficial nature were coated with soot. During this period of study no burns were so extensive as to require hospital admission.

All burns covered with grease, oil, or fat were gently swabbed with cotton pledgets which had been soaked in a particular detergent mixture. No sedation was needed in these relatively minor burns. In many cases, only about two or three cubic centimeters of the mixture were necessary, and only a slight amount of swabbing was required to impregnate the grease or oil layer with the detergent (the heavier the type of grease, the greater was the amount of dispersing force needed). Sterile water was then allowed to flow over the burned area, with or without the gentlest of swabbing. The detergent and the contaminating agents were easily washed away in almost all instances, leaving a clean burned area. After gentle drying with a sterile towel, the burn was then ready for the débridement of vesicles and tanning. For evidence that all grease or oil had been completely removed, a good "take" of dye, usually a 2 per cent aqueous gentian violet, was attained at the first application. Dyed areas also seemed to show a tendency to dry more quickly, and areas usually difficult and slow to stain, such as débrided vesicles and other denuded portions, took up the dye as quickly or more quickly than the adjacent, easily coated areas.

The agents employed caused neither symptoms nor signs of local irritation or pain. Indeed, some of the preparations appeared even soothing in nature.

#### CONCLUSIONS

1. Most workers are of the opinion that vigorous cleansing methods have no place in the preliminary treatment of burns because (a) anes-



thetia is required, (b) shock is thereby increased, and (c) injury to remaining healthy tissue results from scrubbing and the use of irritating cleansing agents.

2. In many burns the tanning or coagulation method of local treatment would seem to possess the advantages of (a) simplicity of application, (b) prevention of fluid, electrolyte, and protein loss from the burned area, (c) prevention of subsequent exogenous infection, provided proper aftercare of the eschar is carried out, (d) rapid easing of pain, and (e) the facilitation of subsequent nursing and transportation. Infection arising from beneath the eschar speaks for the inadequacy of preliminary cleansing procedures. More recently, methods of treatment other than tanning have been recommended. These also have been discussed.

3. Certain of the synthetic detergents, employed in one of several combinations, act as cleansing agents in the local treatment of burns. Their unique properties which make them superior to other cleansing agents are (a) their ability to penetrate and "solubilize" substances such as greases, oils, and fats, as well as particulate matter; these types of contaminants are thus rendered more easily removable by water; (b) their lack of either irritating or noticeable tissue-damaging properties as employed; (c) their antiseptic nature; and (d) the fact that, after all grease, including the normal skin oils, is removed, the subsequent "take" of dye or tanning agent is rendered easier and a proper eschar more readily formed.

4. The principle of employing a penetrant detergent, such as sulfonated petroleum, as a carrier for other more powerful detergents is especially valuable, in so far as it greatly diminishes the amount of mechanical dispersion required to distribute the cleansing solution uniformly throughout an oil or grease layer.

5. In clinical tests with a number of detergent mixtures, performed both on controls with normal, intact skin, and on twenty-five patients with relatively mild, second degree burns, the properties listed above were substantiated. More than three-quarters of the burns when first observed in the emergency service of a metropolitan hospital were covered with grease, oil, fats, or ointments. It is in this group of cases, especially, that the action of the synthetic detergents is best demonstrated.

6. Burns covered with grease and oil, the result of military engagements on sea and land, represent a problem in which the application of these new cleansing agents may be of specific benefit.

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# THE USE OF TANNIC ACID JELLY IN EXPERIMENTAL BURNS

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## INTRODUCTION

THE importance of the proper emergency treatment of burns has been greatly accentuated by the marked increase in this type of injury in modern warfare. Military experience in the past two years has focused attention on the criticism made even before the present war, that tanning burned skin encouraged the spread of infection beneath the tanned area. It has also been emphasized recently that tanning is undesirable about the neck, face, and genitals and about joints where full range of motion might be limited by an inelastic eschar. In addition, tanning which completely surrounds an extremity may, of course, be dangerous because of constriction by an encircling eschar.

Tanning agents, however, have done a great deal to lower mortality and to alleviate pain during the first forty-eight hours following severe burns. Their use in first-aid treatment has had wide publicity among thousands of lay people, the services of whom must now be utilized in our medical defense program. Consequently, the indications for the use of such agents should be clarified and understood by civilian as well as military first-aid personnel.

It seemed wise, therefore, to investigate some of the properties of water-soluble tannic acid jelly, since this substance has been widely recommended in the first-aid treatment of burns of the trunk and extremities. This was attempted with the hope of learning under what circumstances such tanning may still be the procedure of choice.

Only the problem of the local first-aid treatment of the burn itself is considered. No attempt will be made in this paper to deal with the problems of shock, chemotherapy, and subsequent treatment of denuded areas.

Investigations were carried out on a 10 per cent tannic acid jelly in a water-soluble base, tragacanth, dispensed under the name of Tanaburn.\*

## MATERIAL AND RESULTS

The following studies were done:

1. Cultures of tanaburn, taken from unselected tubes of the jelly and planted on standard blood agar pour plates, showed no growth.

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\*Manufactured by Tailby-Nason Co., Boston, Mass.

2. Standard blood agar pour plates were made incorporating tanaburn in approximately a 0.3 per cent solution, well dispersed in the liquid agar before the plates were poured. These were inoculated with pure cultures of (1) beta hemolytic streptococci, (2) *Staphylococcus aureus*, and (3) *Bacillus coli*. Control plates were poured with each of these organisms, leaving out the tanaburn. In each instance, the number of colonies present at the end of twenty-four and forty-eight hours in the tanaburn pour plates was equal to the number in the control plates.

3. A pure culture of beta hemolytic streptococci in dextrose broth was inoculated directly into tanaburn itself in a sterile test tube. This mixture was incubated and streak plates were made at six, twenty-four, and forty-eight hours. There was no growth in any of these preparations. It is probably not fair here to conclude that the tanaburn was bactericidal for the organisms in the absence of any media to support their growth.

4. The action of tanaburn on normal and infected burned skin when applied almost immediately after the burn was studied as follows: The chest and abdomen of an anesthetized dog were shaved. Standard burns were induced with an ordinary Bunsen burner flame, each area being exposed to the flame for approximately two minutes. This was sufficient to produce discoloration, blistering, and visible weeping of the burned area. At the conclusion of the experiment, the animal was sacrificed.

Four areas were burned as shown in Fig. 1 and treated as follows:

- (a) Burned, infected with beta hemolytic streptococci, covered with a thick layer of tanaburn, and a dry sterile dressing applied
- (b) Burned and covered with a dry sterile dressing
- (c) Burned, infected as in (a) with beta hemolytic streptococci, and covered with a dry sterile dressing
- (d) Burned, covered with a layer of tanaburn, and a dry sterile dressing applied (not infected).

Cultures were made by swabbing the skin surface and introducing the swab together with a small piece of skin, removed under aseptic precautions, into dextrose broth. The broth cultures were incubated two hours, and standard blood agar pour plates were made and examined at forty-eight hours. The results are shown in Table I. The cultures from the burned, infected, and tanned skin at one, three, five, and twelve hours, respectively, were saved, incubated forty-eight hours longer, and then streaked onto blood agar plates. The results are shown in Table II.

These experiments were then repeated on another animal, using boiling water burns and a different strain of hemolytic streptococci. Three areas were burned as illustrated in Fig. 2. Circulating boiling water was applied to the skin in each area for from one to two minutes, using

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TABLE I

CULTURES AT 2 HR.	GROWTH AT 48 HR. (POUR PLATES)
1. Normal skin	1. Abundant growth of <i>Staphylococcus aureus</i> and <i>diphtheroids</i>
2. Burned skin at five hours each	2. No growth
3. Burned and tanned skin at five hours each	3. No growth
4. Burned and infected skin at five hours each	4. 25 to 30 colonies of beta hemolytic streptococci
5. Burned, infected, and tanned skin at one hour each	5. No growth
6. Burned, infected, and tanned skin at three hours each	6. No growth
7. Burned, infected, and tanned skin at five hours each	7. No growth
8. Burned, infected, and tanned skin at five hours each	8. No growth

TABLE II

CULTURES AT 48 HR.	GROWTH 48 HR. LATER (STREAK PLATE)
5. Burned, infected, and tanned skin at one hour each	5. No beta hemolytic streptococci
6. Burned, infected, and tanned skin at three hours each	6. 25 colonies of beta hemolytic streptococci
7. Burned, infected, and tanned skin at five hours each	7. Abundant growth of beta hemolytic streptococci
8. Burned, infected, and tanned skin at twelve hours each	8. Very abundant growth of beta hemolytic streptococci

TABLE III

CULTURES AT 2 HR.	GROWTH IN 48 HR. (POUR PLATES)
1. Burned skin at five hours each	1. No growth
2. Burned and tanned skin at five hours each	2. No growth
3. Burned, tanned, and infected skin at one hour each	3. No growth
4. Burned, tanned, and infected skin at three hours each	4. No growth
5. Burned, tanned, and infected skin at five hours each	5. 10 colonies of beta hemolytic streptococci
6. Burned, tanned, and infected skin at twelve hours each	6. 35 colonies of beta hemolytic streptococci

the device illustrated in Fig. 3. This was sufficient again to produce discoloration, vesiculation, and blistering of the skin. In this animal the areas were treated as follows:

(a) Burned and covered with a dry sterile dressing.

(b) Burned and covered with a layer of tanaburn and a dry sterile dressing (not infected).

(c) Burned, infected with beta hemolytic streptococci, and covered with a layer of tanaburn and a dry sterile dressing. Cultures of the burned skin similar to those made in the first experiment were made with results as shown in Table III.

Broth cultures in this instance were also kept, incubated forty-eight hours longer, and then streaked onto blood agar plates. The results are shown in Table IV.

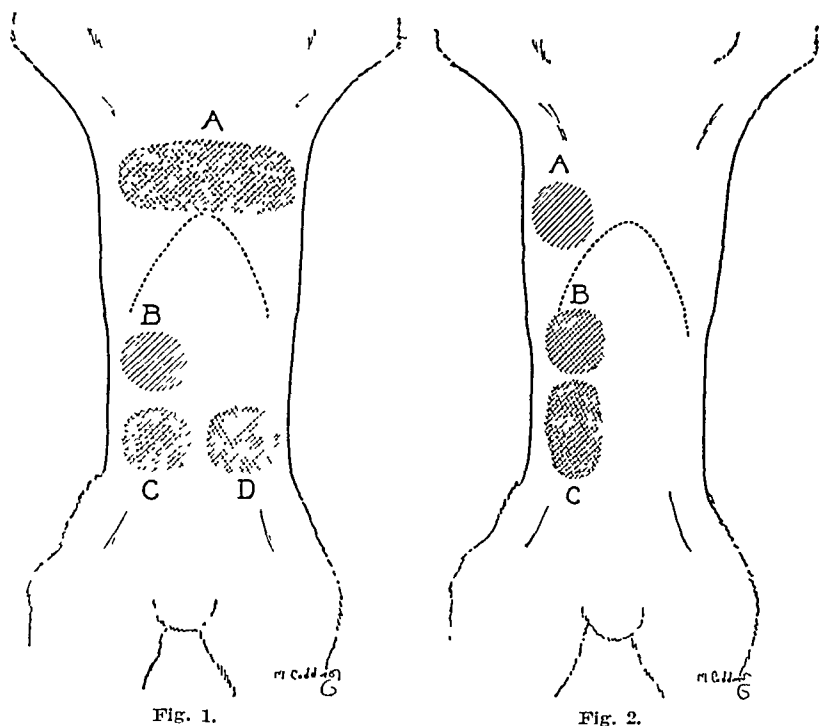


Fig. 1.—Experimental burns with Bunsen burner flame. A, Burned, infected, and tanned; B, burned; C, burned and infected; D, burned and tanned.  
 Fig. 2.—Experimental burns with boiling water. A, Burned; B, burned and tanned; C, burned, infected, and tanned.

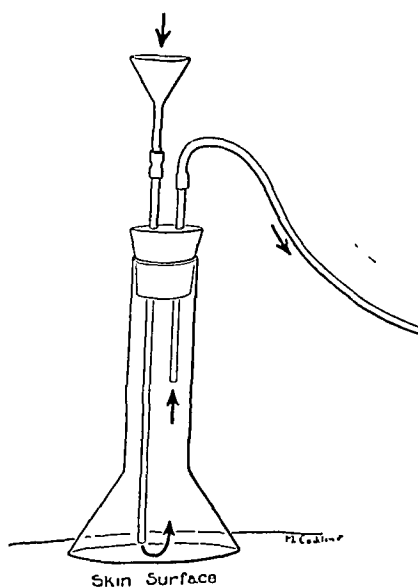


Fig. 3.—Device for applying circulating boiling water to animal skin.

5. Tanaburn begins to form an eschar on burned skin between three and five hours. This is quite thick, pliable, and cannot be washed or wiped from the skin at twelve hours.

6. Tanning the burned skin has no effect on the amount of subcutaneous edema present at the end of five hours.

#### COMMENT

These experiments seem to indicate that 10 per cent tannic acid jelly applied to infected burns of the skin exerts a transient bacteriostatic effect for periods up to three hours. However, after this length of time, bacterial growth proceeds readily. Also, after three to five hours an eschar forms which becomes more and more difficult to remove.

Burns covered immediately with a dry sterile dressing and burns which were tanned and then covered both remained sterile. Presumably the burn itself killed the organisms shown to be present on the normal skin control. It is during the period between the acquisition of the burn and the arrival of medical attention that the burn becomes infected—from surrounding skin, clothing, foreign bodies, and exposure to air contamination. In the laboratory this course of events was insured by actual inoculation of the burn with virulent organisms.

The ideal clinical first-aid local treatment of burns would consist in immediate application and maintenance of an adequate sterile and protective dressing until hospital care could be instituted. This is rarely possible, of course, outside of the experimental laboratory, and certainly not in the great majority of military or civilian wartime casualties. To condemn uniformly the tanning of burns is being idealistic. During war, the problems raised by individual lesions become secondary in importance to the adequate handling of a great volume of injuries. Under the conditions imposed by mass burning in crowded areas, the treatment must not only be efficacious, but also feasible.

Is there a place for tannic acid jelly in these circumstances? It is easy to apply. It has desirable analgesic properties. It is readily available. When satisfactorily employed, it forms a pliable, comfortable eschar which obviates the necessity for repeated painful dressings. However, its general use by the laity in large numbers of civilian or military casualties cannot be recommended without specific limitations. Although definite transient bacteriostatic properties appear to be present, 10 per cent tannic acid jelly is not bactericidal when used on infected burns. It is possible, therefore, that it may give the patient comfort and aid him physiologically through the first forty-eight hours after the burn, only to leave him with the subsequent severe complication of sepsis.

Experimental evidence indicates that tannic acid jelly should be used as a first-aid measure only when it can be applied almost immediately after the burn is incurred and only to burns which are not contaminated. In active, well-equipped first-aid stations near the scene



TABLE IV

CULTURES AT 48 HR.	GROWTH 48 HR. LATER (STREAK PLATE)
3. Burned, tanned, and infected skin at one hour each	3. Few colonies of beta hemolytic streptococci
4. Burned, tanned, and infected skin at three hours each	4. Many colonies of beta hemolytic streptococci
5. Burned, tanned, and infected skin at five hours each	5. Abundant growth of beta hemolytic streptococci
6. Burned, tanned, and infected skin at twelve hours each	6. Very abundant growth of beta hemolytic streptococci

5. Observations were also made on the rate of formation of the eschar on these burned areas of skin. At the end of one and three hours after application of a thick layer of tanaburn, the eschar could be simply wiped or washed off with ease; at the end of five hours it could be washed off with some difficulty; and at the end of twelve hours a definite eschar had formed which could not be wiped off but had to be peeled off in a layer.

6. Microscopic sections stained with eosin and methylene blue were made of (1) burned, (2) burned and tanned, (3) burned and infected, and (4) burned, infected, and tanned skin all taken at five hours after burning and fixed immediately in Zenker's solution. All of these sections showed comparable amounts of subcutaneous edema. No distinction could be made microscopically between the tanned and the untanned burned skin. In none of the sections were microorganisms visible.

#### SUMMARY

1. Tanaburn, a 10 per cent tannic acid jelly in a water-soluble base, in itself is sterile.

2. A small amount of tanaburn exerted no bacteriostatic effect on pure cultures of beta hemolytic streptococci, *Staphylococcus aureus*, and *Bacillus coli* growing in blood agar media.

3. Beta hemolytic streptococci will not grow in tanaburn alone. This does not mean that tannic acid jelly is bactericidal but that it does not provide a media sufficient to support the growth of the organisms.

4. Beta hemolytic streptococci are readily recultured from burned and infected skin at the end of five hours. If this infected burn is covered with tanaburn, similar cultures taken at one, three, five, and twelve hours and incubated for two hours show no growth. However, if these cultures are allowed to incubate for forty-eight hours, then the three-, five-, and 12-hour cultures show increasing numbers of colonies of beta hemolytic streptococci. Tanaburn, therefore, is not bactericidal for these organisms, since they eventually grow out in profusion, but a definite bacteriostatic effect is evidenced by the absence of growth in the one- and three-hour cultures from both the flame and hot water burns.

# THE EFFECTS OF THE APPLICATION OF A TOURNIQUET ON THE GENERAL RESPONSE TO GROSS TRAUMA TO AN EXTREMITY

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IN EXPERIMENTS<sup>1, 2</sup> recently performed in which a mechanical press was applied to an extremity for an extended period (fifteen hours), it was found that the animals succumbed even though plasma equal in quantity to that which was lost locally was administered intravenously. This was not the finding in a number of the experiments in which the press was applied for a shorter time (five hours). Since the pressure which was exerted on the tissues was the same in the two groups of experiments, the results indicated that the prolonged period of local ischemia and anemia was responsible for the difference in the severity of the general effects. In view of these observations in experiments on crush injuries, it was decided to study the effects of applying a tourniquet to an extremity after trauma to the soft parts had been produced. These experiments were compared with others in which a similar injury was caused, but no tourniquet was applied. In all the experiments, early death was prevented by the intravenous administration of blood plasma.

## METHODS AND RESULTS

Large animals were used in all the experiments. Pain was prevented by the administration of nembutal and morphine. Trauma was produced by striking the soft parts of one of the posterior extremities many blows with a hammer. The number of blows varied somewhat according to the ease with which the muscular tissue became damaged. The usual time required for the carrying out of the trauma was about four minutes. The femur was not fractured and an attempt was made not to cause a break in the skin.

Ten animals served as controls, no tourniquet being used. In the remaining ten animals a rubber tourniquet was applied tightly around the upper part of the thigh, proximal to the upper level of the trauma, as soon as the infliction of trauma was terminated. An attempt was made to exclude the arterial inflow as well as the venous return of the extremity. The period that the tourniquet was left in place was five hours.

In the control experiments blood plasma was administered intravenously two hours after the traumatization of the extremity. The rate

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of a disaster this may occasionally be possible. Old and contaminated wounds should simply be covered with a sterile or the cleanest possible dressing and pain alleviated with large doses of sedatives until careful cleansing is possible. If the tannic acid jelly has already been applied to contaminated burns or to burns more than two hours old, then every effort should be made to remove it within three to five hours of the time of application, and local treatment suitable for any infected wound of this type should be carried out, supplemented, of course, by sulfonamide and supportive therapy.

TABLE I

SHOWING THE EFFECTS OF TRAUMA TO AN EXTREMITY AND OF PLASMA THERAPY  
(NO TOURNIQUET)

EXPERIMENT NO.	ARTERIAL PRESSURE (MM. HG)		HEMATOCRIT READING		PULSE RATE PER MIN.		THERAPY PLASMA PER CENT BODY WEIGHT	RESULT
	CON- TROL	6 S HR. AFTER PLASMA BEGUN	CON- TROL	6 S HR. AFTER PLASMA BEGUN	CON- TROL	6 S HR. AFTER PLASMA BEGUN		
1	120	105	46.3	32.7	124	184	5	Died on twelfth day
2	115	125	55.4	32.0	140	194	5	Recovered
3	115	105	53.8	45.0	116	180	5	Recovered
4	110	115	56.0	34.0	136	160	5	Recovered
5	115	120	52.0	39.5	96	220	5	Recovered
6	120	100	56.6	39.0	112	194	5	Recovered
7	120	120	53.6	24.0	140	196	5	Recovered
8	115	115	41.7	29.5	116	192	5	Died after 90 hours
9	115	95	55.0	38.3	92	200	5	Recovered
10	110	120	50.2	39.0	104	180	5	Recovered

instead of the usual 5 per cent. The survival period did not appear to be lengthened by the administration of the larger quantity of plasma. The average amount of plasma injected in the ten experiments equalled 7.3 per cent of the body weight of the recipient and the average regional loss of fluid equalled 7.8 per cent of the body weight. This shows very clearly that the regional loss of fluid in experiments of this type in which a tourniquet and replacement therapy were used was not responsible for the uniformly fatal results. Some of the results are given in Table II.

Whereas no significant decline in the arterial pressure occurred in the control experiments, a marked decline was found following the removal of the tourniquet in the experiments in which the constriction was used. This occurred despite the fact that the plasma was introduced at a rather rapid rate in some of the experiments. There was an acceleration of the pulse rate and a decline in the hematocrit reading. In contrast to the observations in the control experiments, the plasma creatine and the non-protein nitrogen became elevated. The urine became darker in color and a moderate number of erythrocytes and granular casts were seen on microscopic examination.

## DISCUSSION

An attempt was made to cause the same amount of injury to tissues in all of the experiments. The fact that death occurred in all the experiments in which a tourniquet was applied to the injured extremity, whereas eight of the ten control animals survived, appears to be of significance. The survival period of the two control animals which died was longer than that of any of the animals in the other group. The results show very clearly that the prolonged application of a tourniquet to an injured extremity results in harmful effects

of injection was equivalent to 1 per cent of the body weight of the recipient per hour. In the experiments in which a tourniquet was used, the injection of plasma was begun simultaneously with the removal of the tourniquet. The arterial blood pressure was essentially normal at the time.

The quantity of plasma that was given in most experiments equalled 5 per cent of the total body weight of the recipient. This figure was chosen because it was found in earlier experiments by one of us<sup>3</sup> and by Parsons and Phemister<sup>4</sup> that this type and degree of trauma result in the regional loss of fluid (mainly whole blood) equal to approximately 5 per cent of the body weight, which is about one-half of the total blood volume. In some of the experiments in which a tourniquet was applied, the amount of fluid which was given was greater.

The various studies which were performed included the arterial blood pressure, the hematocrit reading, the pulse rate, the plasma creatine and creatinine, the urinary creatine and creatinine, the nonprotein nitrogen, and gross and microscopic examinations of the urine. The methods which were employed have been enumerated previously.<sup>1</sup>

The animals were observed until death or recovery took place. If death occurred, the local loss of fluid into and near the injured area was determined by the bisection method<sup>3</sup> that has been described previously.

As has been stated, ten control experiments were performed. The extremity was traumatized but no tourniquet was applied. Eight of the ten animals recovered, one animal dying at the end of ninety hours and the other on the twelfth day. Previous experience<sup>3</sup> with this method of producing injury would indicate that most of the animals would have died had plasma not been injected. Examination of the animal which died at ninety hours showed bilateral pneumonia and an abscess of the thigh. The animal which died on the twelfth day also had an abscess of the thigh. Some of the results of these experiments are given in Table I.

Alterations which were observed in the first ten hours following the traumatization of the control animals included an elevation in the pulse rate and a decrease in the hematocrit reading. The latter alteration was probably due, mainly, to the injected plasma. There was very little alteration in the arterial blood pressure, the plasma creatine, and the nonprotein nitrogen. In some instances the traumatization was followed by a slightly reddish discoloration of the urine and by the presence of a few erythrocytes and granular casts in the urine.

The findings in the ten experiments in which a tourniquet was used differed from the controls in a number of respects. All the animals died, the survival period following the removal of the tourniquet varying from three to thirty-six hours, the average being approximately fourteen hours. Five of the ten animals were given plasma in an amount which equalled 9 per cent or more of the body weight of the recipient

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(NO TOURNIQUET)

EXPERIMENT NO.	ARTERIAL PRESSURE (MM. HG)		HEMATOCRIT READING		PULSE RATE PER MIN.		THERAPY PLASMA PER CENT BODY WEIGHT	RESULT
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instead of the usual 5 per cent. The survival period did not appear to be lengthened by the administration of the larger quantity of plasma. The average amount of plasma injected in the ten experiments equalled 7.3 per cent of the body weight of the recipient and the average regional loss of fluid equalled 7.8 per cent of the body weight. This shows very clearly that the regional loss of fluid in experiments of this type in which a tourniquet and replacement therapy were used was not responsible for the uniformly fatal results. Some of the results are given in Table II.

Whereas no significant decline in the arterial pressure occurred in the control experiments, a marked decline was found following the removal of the tourniquet in the experiments in which the constriction was used. This occurred despite the fact that the plasma was introduced at a rather rapid rate in some of the experiments. There was an acceleration of the pulse rate and a decline in the hematocrit reading. In contrast to the observations in the control experiments, the plasma creatine and the non-protein nitrogen became elevated. The urine became darker in color and a moderate number of erythrocytes and granular casts were seen on microscopic examination.

## DISCUSSION

An attempt was made to cause the same amount of injury to tissues in all of the experiments. The fact that death occurred in all the experiments in which a tourniquet was applied to the injured extremity, whereas eight of the ten control animals survived, appears to be of significance. The survival period of the two control animals which died was longer than that of any of the animals in the other group. The results show very clearly that the prolonged application of a tourniquet to an injured extremity results in harmful effects.

TABLE II  
SHOWING THE EFFECTS OF TRAUMA TO AN EXTREMITY, OF THE APPLICATION OF A TOURNIQUET, AND OF PLASMA THERAPY

EXPERIMENT NO.	ARTERIAL PRESSURE MM. HG		HEMATOCRIT READING		PULSE RATE PER MIN.		HOURS TOURNIQUET APPLIED	THERAPY PLASMA PER CENT BODY WEIGHT	SURVIVAL AFTER TOURNIQUET REMOVED (HR.)	FLUID LOSS PER CENT BODY WEIGHT (REGIONAL)
	CONTROL	4-6 HR. AFTER TOURNI- QUET REMOVED	CONTROL	4-6 HR. AFTER TOURNI- QUET REMOVED	CONTROL	4-6 HR. AFTER TOURNI- QUET REMOVED				
1	115	50	52.3	39.8	144	200±	5	9.2	13	8.31
2	125	60	55.8	50.8	136	200+	5	10.4	26	11.63
3	115	80	41.2	27.0	160	186	5	10.0	13	9.59
4	120	0	38.0	36.4	140	140	5	9.8	3	5.32
5	130	80	53.2	30.3	146	200+	5	9.0	6	9.14
6	110	50	38.3	27.4	108	200+	5	5.0	14	5.15
7	105	75	36.4	30.0	148	164	5	5.0	36	4.58
8	120	70	53.0	41.8	124	200+	5	5.0	13	8.68
9	110	70	38.3	34.0	128	184	5	5.0	14	7.91
10	115	45			136	200+	5	5.0	5.5	9.36

The findings recorded here receive support from previous experimental and clinical observations. A number of observers have produced shock by interfering with the circulation to a large portion of the body for a considerable time. Wilson and Roome<sup>5</sup> found that the removal of a tourniquet is followed by the passage of a large amount of the blood volume into the dilated blood vessels of the extremity. As a result of clinical observations and reports in World War I, Cannon<sup>6</sup> stressed the dangers of the removal of a tourniquet which had been in place for hours.

It is obvious because of the present and of the previous studies that a tourniquet should be used for the control of bleeding only if other means are not available or will not suffice. If the extremity is badly damaged and if a tourniquet has been in place for several hours when the patient reaches a point where definitive treatment may be employed, amputation is usually advisable. Our previous experiments on crush injuries, as well as the observations of Allen<sup>7</sup> and of Brooks and Duncan,<sup>8</sup> indicate that the harmful effects of a tourniquet will be lessened if the temperature of the part distal to the constriction is lowered by the application of ice. Unfortunately, under emergency conditions, means for lowering the temperature are not usually available.

#### SUMMARY

Experimental findings are presented which show that the prolonged application of a tourniquet to an injured extremity greatly lessens the chances of survival of the animal.

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# GRADUAL OCCLUSION OF THE MESENTERIC VESSELS

## EXPERIMENTAL STUDY

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WHEN a thrombus forms very slowly, collateral circulation has an opportunity to carry the blood supply. Warren and Eberhard<sup>15</sup> have pointed out that a very gradual occlusion of the main mesenteric vessel may, in some instances, result in infarction of the intestine; in other instances there may be temporary symptoms of pain and intestinal hemorrhage; it may even result in no symptoms at all if it forms slowly enough. Narrowing of the mesenteric vessels is not uncommon as a feature of generalized arteriosclerosis.

There have been occasional cases reported in which the main artery was slowly occluded, causing no untoward symptoms during life and no involvement of the intestine at autopsy. Best known of such cases are those of McCallum,<sup>1</sup> Trotter,<sup>2</sup> and Howse.<sup>3</sup>

Councilman,<sup>4</sup> Reich,<sup>5</sup> Davis,<sup>6</sup> Garcia,<sup>7</sup> and Moore<sup>8</sup> reported cases in which the collateral circulation after mesenteric occlusion was sufficient to prevent pathologic changes in the bowel wall, but not sufficient to allow normal function to continue. Intestinal ileus results in such cases. In Moore's case the patient suffered from intestinal obstruction due to a localized area of paralytic ileus caused by occlusion of mesenteric vessels. The blood supply was sufficient to keep the bowel alive, but could not sustain normal function. Following a lateral anastomosis the patient made a complete recovery.

Karcher<sup>9</sup> reported a case in which surgical treatment was not undertaken despite typical symptoms of mesenteric vascular occlusion, because of the poor condition of the patient. In other instances, lack of diagnosis or just watchful waiting with general support of therapy have resulted in a spontaneous recovery. Karcher's patient died from another cause seven weeks after the occlusion had taken place. An autopsy revealed an embolus completely occluding the superior mesenteric artery. The bowel was not infarcted.

Experimental reproduction of a long-term gradual occlusion of the main mesenteric vessels has not, to my knowledge, been previously reported. It is, therefore, of some interest to report the experimental results of such occlusions.

Pearce<sup>10</sup> has recently advocated the use of cellophane for the experimental gradual occlusion of large arteries. Mims Gage<sup>11</sup> has reported

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he experimental production of hypertension by encasing the kidney of a dog in cellophane and allowing it to become constricted over a long period of time.

We have been able to completely occlude the superior mesenteric artery by gradual constriction over a period of four months by the use of cellophane in three of six animals in which this procedure was carried out. A similar procedure, constricting the superior mesenteric vein, was successfully accomplished in two of five attempts.

#### EXPERIMENTAL DATA

Ordinary DuPont cellophane No. 300 P.T. was used. It was soaked in phenol for ten minutes and then alcohol for about one hour before operation. A  $\frac{1}{4}$ -inch wide strip consisting of four folded layers was loosely wrapped about the vessel. The ends were sutured with a silk mattress stitch so that the cellophane hugged the vessel snugly, but did not constrict. The animals were allowed to continue normal existence for four to five months, at which time they were opened for examination. It was noted that the animals in which the superior mesenteric artery was so treated became progressively thinner and lost their appetites. Those animals in which the superior mesenteric vein was wrapped with cellophane at no time showed any ill effects.

*Observations.*—In three of the six animals in which the superior mesenteric artery was wrapped with cellophane, it was found that the artery had become completely occluded over the course of sixteen to

TABLE I  
GRADUAL OCCLUSION OF MAIN MESENTERIC VESSELS BY CELLOPHANE

	DATE CELLOPHANE APPLIED	DOG NO.	DATE OF LAPAROTOMY OR SACRIFICE OF ANIMAL	FINDINGS
Arterial	11/14/40	1C	3/18/41	Occlusion not complete
	12/18/40	4C	4/21/41	Occlusion complete; low grade enteritis; thrombosis of small vessels
	1/ 8/41	5C	5/20/41	Occlusion not complete
	1/15/41	7C	6/10/41	Occlusion not complete
	1/15/41	8C	6/10/41	Occlusion complete; enteritis; erosion of mucosa
	11/22/41	9C	6/10/41	Occlusion complete
Venous	11/27/40	2C	3/18/41	Occlusion not complete
	12/18/40	3C	4/21/41	Occlusion not complete
	1/ 8/41	6C	5/20/41	Occlusion not complete
	11/11/41	10C	3/23/42	Occlusion complete
	11/11/41	11C	3/23/42	Occlusion complete

eighteen weeks. In the remaining three animals complete occlusion had not yet taken place. The cellophane had produced a severe degree of tissue irritation, causing extensive changes around the vessel. These changes consisted of a fibroplastic response with purulent or gelatinous fluid encased about the cellophane. The intestinal wall appeared very pale and thin in these animals. Microscopic examination of the intestinal

wall revealed a low-grade enteritis of varying degree in the various specimens, with erosion of the villi and leucocytic infiltration of the remaining mucosa and submucosa. There was no infarction present. However, the small subserosal vessels contained thrombi (Fig. 1). The similarity of the results in the three animals indicated that the lesion in the intestine was directly the result of the gradual occlusion of the superior mesenteric artery. No changes were noted in the intestinal walls of the dogs in which the occlusion was incomplete. Blood pressure readings were not taken.

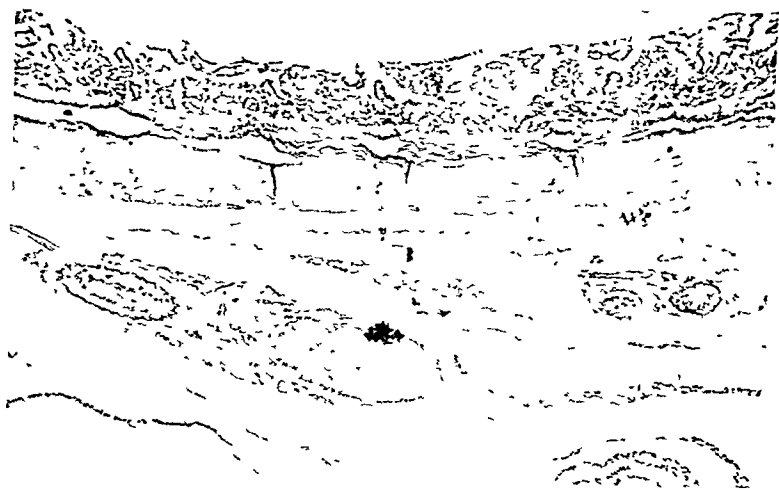


FIG. 1.—Microscopic appearance of small intestine after gradually induced, complete occlusion of the superior mesenteric artery in the dog by cellophane after approximately four months. Note erosion of mucosa, infiltration by polymorphonuclear leucocytes (low-grade enteritis), and thrombosis of small subserosal and intramural vessels. Grossly the intestine appeared markedly anemic with thinned out walls.

It is known that blockage of the lymph channels of the mesentery can produce an ulcerative lesion in the intestine, the microscopic appearance of which is not dissimilar from that described above (Poppe<sup>12</sup>). It is thus possible that the irritative response produced by cellophane may have blocked the lymph channels as well as the arterial supply. Thus, the lesion produced may be the result of either or both, chronic hypoxia and chronic infection with lymphatic blockage.

Gradual occlusion of the superior mesenteric vein resulted in no lesion of the intestine in either of the two animals successfully ligated. However, it was interesting to trace the collateral venous drainage of the intestine, especially since there was no embarrassment of the intestinal circulation. Preparations were made, therefore, for roentgen-ray study by injecting a dilute solution of barium sulfate into one of the small mesenteric veins. The accompanying roentgenogram illustrates the remarkable collateral circulation established as a result of the gradual occlusion. Adhesions were found between the fibroplastic mass around the cellophane and loops of intestine, the omentum, and portion of mesentery. The collateral blood channels established in these adhesions

are well shown in the photographs. An interesting source for collateral circulation was noted in small vessels which apparently traversed the posterior parietal peritoneum and found their way into the kidney (Fig. 2).

The abundance of the collateral supply explains the paucity of symptoms and the absence of circulatory changes associated with the long-



Fig. 2—Result of gradually induced, complete occlusion of the superior mesenteric vein in the dog by cellophane after approximately four months. Illustration shows roentgenogram of specimen injected with dilute barium sulfate solution. The venous tree of the liver (above) received blood from collateral channels which formed about the occlusion. Collateral channels are also shown in the posterior parietal peritoneum and capsule of the kidney. Not shown are further collateral channels found in numerous omental adhesions about the occlusion.

term type of gradual occlusion of the superior mesenteric vein. Twenty cases illustrating this type of total occlusion in man as an incidental necropsy finding associated with no intestinal changes were reported by Laufman and Schemberg.<sup>13</sup>

Felsen<sup>14</sup> has presented clinical and autopsy material illustrating the effects of long-term anoxia due to intestinal vascular sclerosis. He describes a proliferative phase and an obliterative phase in the intra-

mural vessels resulting from gradual occlusion of the mesenteric vessels. In the proliferative phase the intramural vessels are thickened and tortuous, while in the subsequent obliterative phase these capillaries are straightened and rigid, with obliterated terminal arborizations. The experimental observations presented above apparently are commensurate with the obliterative phase with superimposed low-grade inflammation.

#### SUMMARY

Gradual occlusion of the superior mesenteric vessels over a period of four to five months was accomplished in dogs by the use of cellophane bands. Complete occlusion of the superior mesenteric artery was accomplished in two of five attempts. In the remaining animals the vessels were constricted but not completely occluded.

The result of gradual complete occlusion of the superior mesenteric artery was an anemia of the intestinal wall with a superimposed low-grade enteritis. Thrombi were present in the intramural vessels.

Gradual complete occlusion of the superior mesenteric vein resulted in no demonstrable lesion in the intestine. Extensive collateral circulation was established in these animals, including the vascularization of omental adhesions and of the posterior parietal peritoneum.

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## INJECTION OF VARICOSE VEINS

### THE IMPORTANCE AND TECHNIQUE OF INJECTING THE ELEVATED EXTREMITY

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#### INTRODUCTION

WITH the perfection of sclerosing therapy for varicose veins of the lower extremities, surgeons in general have come to avail themselves of this method of varicose vein therapy. McPheeters' writings on the ambulatory injection treatment of varicose veins served to stimulate considerable interest in this mode of management in this country. Since, probably, about 10 per cent of young healthy adults suffer from varicose veins, and since most of these people are engaged in activities which necessitate a minimum of medical care during the treatment, any method which would reduce the number of required injections would be an approach to the ideal injection technique. Everyone who has acquainted himself with the injection technique has come to realize that the necessity of giving as many as twenty injections in those cases in which there are numerous varicose radicals of the main varicose trunk is not an inviting feature to patients. If a method could be found by which the number of injections could be reduced to one or two, a big disadvantage would be overcome. The purpose of this communication is to describe such a method.

Generally, the principle embodied in the obliterative treatment is to maintain the sclerosant in contact with the intima of the vein long enough to produce an intimal inflammation eventuating in thrombus formation and, finally, fibrosis. In the usual method, the varix is injected with the patient in the horizontal or sitting position, several injections being made at different sites at one visit, or single injections being given at successively lower levels at successive visits. Fig. 1A diagrammatically illustrates such an injection. The sclerosant, injected into an engorged vein, does not diffuse, coagulation of the immediately surrounding blood further impeding the spread of the solution. This results in a localized thrombus which can be felt later as a hard, fibrotic lump. Attempts to inject a segment after "stripping" it of its

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blood are often discouraging, since incompetent communicating veins allow the inflow of blood.

The method described in this communication has been employed successfully in a large series of cases on the Surgical Service of the O'Reilly General Hospital, U. S. Army, Springfield, Mo., and in the Surgical Outpatient Clinic of the University of Minnesota Hospital, Minneapolis. With this simple technique, almost all patients have required a single injection, while a few have been given two injections. The effectiveness of this method lies in the principle that a relatively small amount of sclerosant—a few cubic centimeters—when injected into bloodless veins, reduced to capillary spaces, can produce intimal inflammation in all the varices of an extensively varicose venous circulation. The sclerosant is undiluted by blood, and, theoretically, 1 c.c. should be sufficient to sclerose many yards of such collapsed veins.

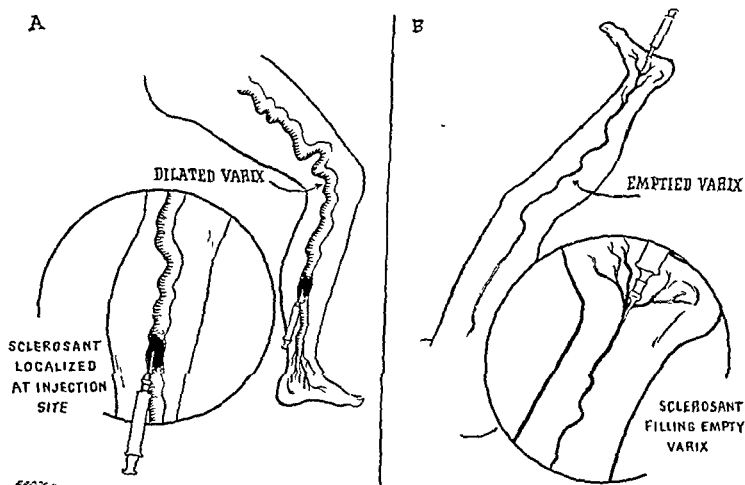


Fig. 1.—The effect of position of the extremity on diffusion of sclerosing solution injected into a varix. A, Extremity dependent, showing localization of sclerosant in varix dilated with blood. The final thrombus develops at the site of injection only. B, Extremity elevated, showing sclerosant flowing through capillary lumen of collapsed varix. The final thrombus develops in the entire vein.

#### INDICATIONS

Before proceeding with varicose vein therapy, certain contraindications must be observed,<sup>2</sup> among which are the following:

- A. Systemic diseases
  - Malignancy
  - Angina pectoris
  - Cerebral thrombosis
  - Myocardial disease
  - Hyperthyroidism
  - Active tuberculosis
  - Acute infectious diseases (including acute upper respiratory infections and tonsillitis)

## B. Local conditions . . .

Lack of patency in the deep venous system

Impairment of arterial circulation

Inflammation or infection of the deep or superficial venous system

Schwartz's test (palpation of a varix below the knee while percussing the saphenous vein in the upper part of the thigh) is positive if an impulse can be palpated below. This indicates incompetence of the valves between the site of palpation and the site of percussion and is always positive in varices of the great saphenous system. The incompetence of the saphenous valves may be verified by the Trendelenburg test. This is performed simply by elevating the affected extremity for a few minutes and then compressing the saphenofemoral junction, while the patient is allowed to stand. If the veins of the leg fill rapidly (within thirty seconds), incompetence of the valves in the communicating veins may be assumed. If a slow filling occurs (over thirty seconds), the communicating system is relatively uninvolved. It may be recalled that there are from one to three communicating veins in the thigh and from fifteen to thirty in the leg. Should additional dilatation of the saphenous system take place when the digital compression of the saphenofemoral junction is removed, one may assume that back pressure in the venous column from the heart to the varix contributes to the vicious cycle.

If the Schwartz and Trendelenburg tests are positive, high interruption of the saphenous vein at the saphenofemoral junction is indicated, providing the deep system is patent. A simple test for patency of the deep venous system is the tolerance, for a few hours, of an elastic bandage wrapped snugly from the ankle to the lower thigh. Perthes' test may also be performed for this purpose. In this test, a tourniquet to compress the superficial veins is placed above the varices and the patient allowed to walk or vigorously exercise the knee. If the varices become more prominent, the deep veins are probably obstructed (negative Perthes' test); if the varices collapse or become less prominent, the deep veins are patent (positive Perthes' test). Mahorner and Ochsner<sup>3</sup> have described a refined segmental Perthes' test.

If high saphenous interruption is found to be indicated, it should be performed before sclerosing therapy is instituted, since back pressure from above will nullify the results expected from even perfect injection technique. The widely accepted operative procedure described by de Takáts<sup>4</sup> carries a 0.3 per cent risk of pulmonary embolism (Faxon and Barrow<sup>5</sup>), but ligation alone will cure about 20 per cent of the patients, the remaining 80 per cent requiring sclerosing injections.

## METHOD

With the patient sitting on the table and the lower extremities on a nearby stool or simply flexed over the side, one of the most distal varicose veins, one usually around the ankle, is selected. A No. 25



blood are often discouraging, since incompetent communicating veins allow the inflow of blood.

The method described in this communication has been employed successfully in a large series of cases on the Surgical Service of the O'Reilly General Hospital, U. S. Army, Springfield, Mo., and in the Surgical Outpatient Clinic of the University of Minnesota Hospital, Minneapolis. With this simple technique, almost all patients have required a single injection, while a few have been given two injections. The effectiveness of this method lies in the principle that a relatively small amount of sclerosant—a few cubic centimeters—when injected into bloodless veins, reduced to capillary spaces, can produce intimal inflammation in all the varices of an extensively varicose venous circulation. The sclerosant is undiluted by blood, and, theoretically, 1 c.c. should be sufficient to sclerose many yards of such collapsed veins.

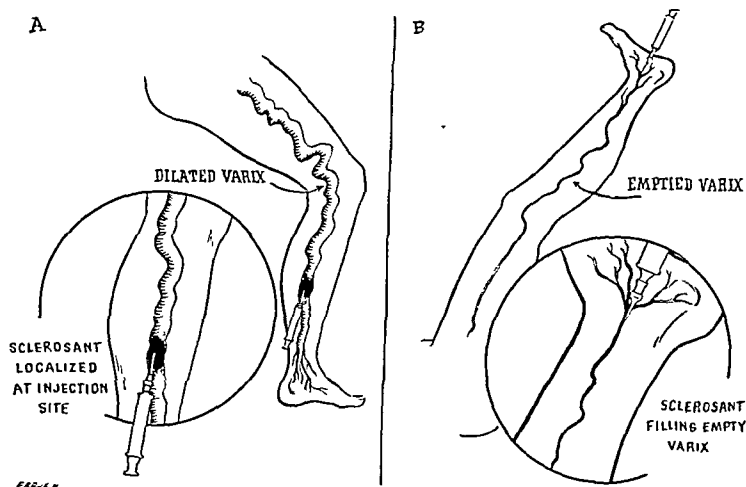


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## SUMMARY

A successful method of sclerosing varicose veins by the injection method is described. With this technique the sclerosant is injected into relatively bloodless veins. Usually, it has been possible to produce thrombosis of the entire varicose system by a single injection of sclerosant.

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gauge needle to which is attached a syringe containing 3 to 5 c.c. of a sclerosing solution is inserted into the vein at the most convenient distal point. With the syringe held firmly in place, but without injecting any of the sclerosant, the patient's lower extremities are brought carefully onto the table; the patient lies horizontally, and the affected extremity is elevated by an assistant to at least  $45^{\circ}$  with the horizontal (Fig. 1B). As much as possible of the blood contained in the veins is permitted to drain into the deep system, and when the extremity appears pale, the sclerosant is injected into the ankle vein and the needle removed. No bleeding occurs from the needle puncture since the point of injection is elevated above the level of venous pressure. A small dry dressing is placed over the puncture site and an elastic bandage wrapped from the ankle to the middle of the thigh. The extremity is then placed on several pillows and the patient allowed to remain in that position for twenty minutes, following which the patient is allowed to be ambulatory. The importance of walking about after this postinjection period has been stressed by Dean and Dulin<sup>6</sup> as a prophylactic against embolism.

Any of the popular sclerosants may be employed. Monoethanolamine oleate (monolate) is an effective agent and causes no slough if perivenous injection takes place (Glasser,<sup>7</sup> Meyer<sup>8</sup>). We have used 5 per cent sodium psylliate (sylnasol), which Biegeleisen<sup>9</sup> showed has a remarkably low toxicity, with equal success. Quinine hydrochloride and urethane has also been found to be an excellent sclerosant.

#### COMMENT

Injection of the sclerosant into the collapsed varix permits a relatively undiluted solution to remain in contact with the intima during the period of elevation of the extremity. The surplus solution flows into the deep venous system where it is diluted and rendered ineffective as a sclerosant. The period of twenty minutes in which the extremity remains elevated and the veins collapsed is sufficient to initiate an intimal reaction which proceeds to thrombosis and, finally, fibrosis. In nearly all of our patients, a single injection has been sufficient; a few patients have required two injections, the second being into a functionally independent varicose system; no patient has required more than two injections for complete thrombosis. If recurrence after sclerosing therapy is due to incomplete injection, the technique suggested in this paper should minimize this possibility.

With the method suggested here there is an appreciably greater periphlebitis produced parallel to the greater venous length which is inflamed and thrombosed. This pain can be adequately controlled with the usual analgesics such as aspirin, phenacetin, or small doses of codeine.

studies made at that time revealed nothing more serious than granular pharyngitis and a healing duodenal ulcer. The pain in the ear was considered to be on the basis of glossopharyngeal neuralgia. The patient was dismissed with instructions to follow a regime for ambulatory patients with ulcer.

The patient was next seen at the clinic on June 18, 1941. The pain in the right ear and the soreness in the right side of the throat had persisted, with increased severity, the pain sometimes awakening the patient at night. Recently there had developed a "paralyzed feeling" in his throat, with some difficulty in swallowing and articulating. He also stated that food particles seemed to lodge at the base of his tongue, on the right side.

Examination disclosed an indurated, submucous nodule on the right side of the tongue, near the base. This nodule was fixed superficially and deeply, and was considered to be malignant. One of the upper deep cervical lymph nodes was enlarged and somewhat firm, suggesting the probability of metastatic involvement. The results of general physical examination were otherwise negative except for a questionable enlargement of the liver. Roentgenograms demonstrated a persistence of a duodenal deformity characteristic of ulcer.

At operation on June 25, 1941, the tumor of the tongue was found to be too extensive for surgical removal. Biopsy was therefore done and fourteen radon seeds were inserted. Seven radon seeds also were inserted into the substance of the enlarged right cervical lymph node which had been ascertained, at the time of operation, to be malignant.

The patient made two subsequent visits to the clinic. On the first of these, August 18, 1941, reduction was noted in the size of the primary lesion of the tongue and of the metastatic nodule in the cervical region. On his last admission, Oct. 11, 1941, the patient complained of pain and tenderness in the right side of the upper part of the abdomen. This pain had some features suggestive of cholecystitis with stones and, on one occasion, had necessitated the use of opiates for relief. It was described as a persistent dull ache with frequent exacerbations of increased severity. Loss of strength and appetite were noted, but not jaundice or fever. Chilly sensations had accompanied one of the attacks of pain.

Examination of the head and neck revealed marked reduction in the size of the primary neoplasm, as well as in that of the metastatic nodule. Opinions regarding the condition of the abdomen were best summarized in the consultant's note: "Tender, nodular, enlarged liver with constant pain past six weeks. Severe attack seven days ago requiring opiates for relief. Considerable loss of strength and weight. Impresses me as metastatic carcinoma of the liver (source?). Believe exploration warranted because of youth and good general condition of patient."

On Oct. 14, 1941, surgical exploration of the abdomen was carried out through a small right rectus incision. The liver was found "to be full of metastatic (tumor) nodules." A small specimen for biopsy was taken from one of these nodules to determine the primary source of the malignancy. Because of the utter hopelessness of the patient's condition no further roentgen therapy was advised. He was dismissed from our care on Oct. 22, 1941.

*Pathologic Aspects.*—Material for study consisted of two small nodules removed at biopsy from the tongue and liver, respectively. These nodules were grayish brown and of rather firm consistency. There was nothing on gross examination, however, to suggest the exact nature of the pathologic process involved. Study of microscopic sections prepared from both lesions presented pictures so similar as to enable one to write a single pathologic description. Under the low-power objective one was struck by the cellularity and manifestly malignant properties of the lesion. In neither instance could the invaded tissue (lingual muscles and hepatic parenchyma) be identified. In both lesions a characteristic arrangement of tumor cells was seen, with a grouping in the form of plugs or cylinders, many of which contained hollow centers

# "CYLINDROMA" (ADENOCARCINOMA, CYLINDROMA TYPE)

## REPORT OF TWO CASES WITH METASTASIS

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IN A recent review of primary tumors of the submaxillary gland<sup>2</sup> we called attention to the frequent incidence, in this location, of a type of neoplasm termed "cylindroma." It was found that throughout the literature in general, and in many of the older cases of our own series in particular, this neoplasm was confused frequently with "mixed tumor." It was observed, in our series, that these cylindromas (adenocarcinomas of cylindroma type) were associated with an extremely high incidence of recurrence, even after radical operative procedures. Infiltrative tendencies were most pronounced with special reference to perineural lymphatic involvement. Metastasis was not infrequent and the prognosis, in general, proved unfavorable not only in those instances in which the neoplasm was a pure cylindroma but also in our small group of examples showing transition to the mixed tumor type.

During preparation of the aforementioned review two additional examples of "cylindromas" came under our observation. In one case the tumor had its origin in the tongue; in the other the primary site could not be ascertained with certainty, but the parotid gland appeared to be the probable source. In reporting these two cases it is not our purpose to review the literature or to enter into controversies regarding histogenesis. Our wish is merely to reemphasize the dangerous potentialities of this particular type of malignant process and the importance of distinguishing it from the ordinary mixed type tumors which have a vastly different prognosis.

### REPORT OF CASES

CASE 1.—A married white man, 35 years old, first registered at the Mayo Clinic on June 17, 1939, complaining of pain in the right ear of four years' duration. The family and personal histories were irrelevant. Previous operations had included appendectomy in 1922 and tonsillectomy in 1938. The condition of which the patient complained had begun rather insidiously, with intermittent pain in the right ear, in 1935. Just prior to the onset of pain the patient had been swimming much and to this he had attributed his trouble. The pain continued, however, and became constant in character. Usually it was a dull ache, but as time went on, sharp exacerbations began to occur at irregular intervals. Tonsillectomy had been performed but had given him practically no relief from symptoms. During the year prior to his admission, soreness had developed in the right side of the throat. At about this time the patient observed that chewing aggravated the pain in his right ear. He complained of nothing else except mild dyspepsia of some years' duration. Extensive

studies made at that time revealed nothing more serious than granular pharyngitis and a healing duodenal ulcer. The pain in the ear was considered to be on the basis of glossopharyngeal neuralgia. The patient was dismissed with instructions to follow a regime for ambulatory patients with ulcer.

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On Oct. 14, 1941, surgical exploration of the abdomen was carried out through a small right rectus incision. The liver was found "to be full of metastatic (tumor) nodules." A small specimen for biopsy was taken from one of these nodules to determine the primary source of the malignancy. Because of the utter hopelessness of the patient's condition no further roentgen therapy was advised. He was dismissed from our care on Oct. 22, 1941.

*Pathologic Aspects.*—Material for study consisted of two small nodules removed at biopsy from the tongue and liver, respectively. These nodules were grayish brown and of rather firm consistency. There was nothing on gross examination, however, to suggest the exact nature of the pathologic process involved. Study of microscopic sections prepared from both lesions presented pictures so similar as to enable one to write a single pathologic description. Under the low-power objective one was struck by the cellularity and manifestly malignant properties of the lesion. In neither instance could the invaded tissue (lingual muscles and hepatic parenchyma) be identified. In both lesions a characteristic arrangement of tumor cells was seen, with a grouping in the form of plugs or cylinders, many of which contained hollow centers

# "CYLINDROMA" (ADENOCARCINOMA, CYLINDROMA TYPE)

## REPORT OF TWO CASES WITH METASTASIS

MALCOLM B. DOCKERTY, M.D., AND CHARLES W. MAYO, M.D.  
ROCHESTER, MINN.

*(From the Division of Surgical Pathology, and the Division of Surgery, Mayo Clinic)*

**I**N A recent review of primary tumors of the submaxillary gland<sup>2</sup> we called attention to the frequent incidence, in this location, of a type of neoplasm termed "cylindroma." It was found that throughout the literature in general, and in many of the older cases of our own series in particular, this neoplasm was confused frequently with "mixed tumor." It was observed, in our series, that these cylindromas (adenocarcinomas of cylindroma type) were associated with an extremely high incidence of recurrence, even after radical operative procedures. Infiltrative tendencies were most pronounced with special reference to perineural lymphatic involvement. Metastasis was not infrequent and the prognosis, in general, proved unfavorable not only in those instances in which the neoplasm was a pure cylindroma but also in our small group of examples showing transition to the mixed tumor type.

During preparation of the aforementioned review two additional examples of "cylindromas" came under our observation. In one case the tumor had its origin in the tongue; in the other the primary site could not be ascertained with certainty, but the parotid gland appeared to be the probable source. In reporting these two cases it is not our purpose to review the literature or to enter into controversies regarding histogenesis. Our wish is merely to reemphasize the dangerous potentialities of this particular type of malignant process and the importance of distinguishing it from the ordinary mixed type tumors which have a vastly different prognosis.

### REPORT OF CASES

**CASE 1.**—A married white man, 35 years old, first registered at the Mayo Clinic on June 17, 1939, complaining of pain in the right ear of four years' duration. The family and personal histories were irrelevant. Previous operations had included appendectomy in 1922 and tonsillectomy in 1938. The condition of which the patient complained had begun rather insidiously, with intermittent pain in the right ear, in 1935. Just prior to the onset of pain the patient had been swimming much and to this he had attributed his trouble. The pain continued, however, and became constant in character. Usually it was a dull ache, but as time went on, sharp exacerbations began to occur at irregular intervals. Tonsillectomy had been performed but had given him practically no relief from symptoms. During the year prior to his admission, soreness had developed in the right side of the throat. At about this time the patient observed that chewing aggravated the pain in his right ear. He complained of nothing else except mild dyspepsia of some years' duration. Extensive

studies made at that time revealed nothing more serious than granular pharyngitis and a healing duodenal ulcer. The pain in the ear was considered to be on the basis of glossopharyngeal neuralgia. The patient was dismissed with instructions to follow a regime for ambulatory patients with ulcer.

The patient was next seen at the clinic on June 18, 1941. The pain in the right ear and the soreness in the right side of the throat had persisted, with increased severity, the pain sometimes awakening the patient at night. Recently there had developed a "paralyzed feeling" in his throat, with some difficulty in swallowing and articulating. He also stated that food particles seemed to lodge at the base of his tongue, on the right side.

Examination disclosed an indurated, submucous nodule on the right side of the tongue, near the base. This nodule was fixed superficially and deeply, and was considered to be malignant. One of the upper deep cervical lymph nodes was enlarged and somewhat firm, suggesting the probability of metastatic involvement. The results of general physical examination were otherwise negative except for a questionable enlargement of the liver. Roentgenograms demonstrated a persistence of a duodenal deformity characteristic of ulcer.

At operation on June 25, 1941, the tumor of the tongue was found to be too extensive for surgical removal. Biopsy was therefore done and fourteen radon seeds were inserted. Seven radon seeds also were inserted into the substance of the enlarged right cervical lymph node which had been ascertained, at the time of operation, to be malignant.

The patient made two subsequent visits to the clinic. On the first of these, August 18, 1941, reduction was noted in the size of the primary lesion of the tongue and of the metastatic nodule in the cervical region. On his last admission, Oct. 11, 1941, the patient complained of pain and tenderness in the right side of the upper part of the abdomen. This pain had some features suggestive of cholecystitis with stones and, on one occasion, had necessitated the use of opiates for relief. It was described as a persistent dull ache with frequent exacerbations of increased severity. Loss of strength and appetite were noted, but not jaundice or fever. Chilly sensations had accompanied one of the attacks of pain.

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was performed in an effort to eradicate the neoplastic tissue, which proved to be grade 2 adenocarcinoma of the cylindroma type. Postoperatively, intensive roentgen therapy was administered. The patient returned on four occasions for further observations and continuance of roentgen therapy. On her fourth admission (July 5, 1939), she complained of preauricular tenderness and a nodule in the mastoid region. Examination disclosed several zones of apparently recurrent neoplastic tissue in the preauricular and postauricular areas. These were treated by excision (cautery). Needles containing radium were inserted locally. Microscopically, the nodules of tissue removed again were typical of adenocarcinoma of the cylindroma type.

During the patient's three visits to the clinic, from 1939 to 1941, it was apparent that the disease had been arrested locally. On July 9, 1940, an enlarged right cervical lymph node was removed. This proved to be inflammatory. The patient's last admission was on March 9, 1942. She sought attention because of several small lumps which had recently appeared in the right side of the neck. These nodules had been somewhat tender. Examination disclosed the presence of two enlarged firm nodules in the right upper cervical region. There was no evidence of local recurrence of the malignant process.

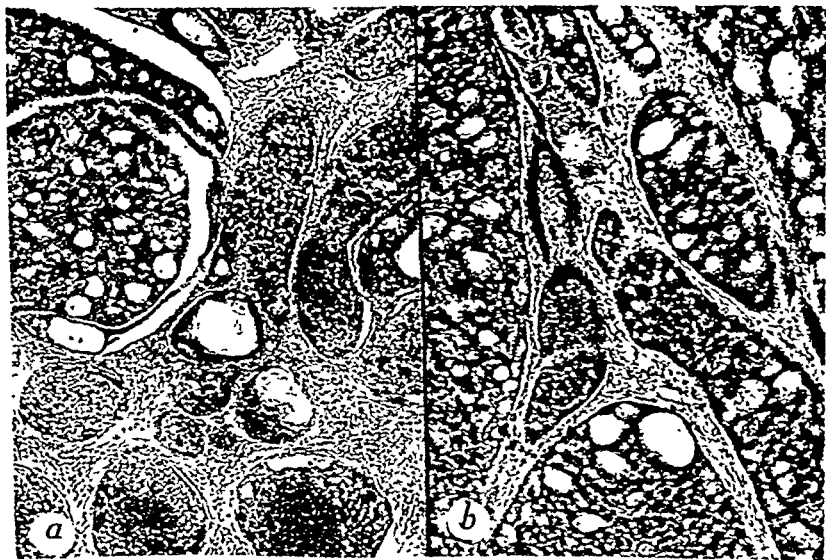


Fig. 2—*a*, Adenocarcinoma, grade 2, cylindroma type; the primary lesion shows pronounced cellularity with a veritable honeycombing of the cylinders which vary considerably in size (hematoxylin and eosin  $\times 60$ ); *b*, the metastatic lesion presents a picture almost identical to that of the primary neoplasm; some of the "acini" are filled with mucus; in others the spaces appear empty (hematoxylin and eosin  $\times 60$ ).

At operation on March 10, 1942, these nodes were removed in a block dissection involving the right cervical chain of nodes. One of the enlarged nodules proved to be an inflammatory lymph node. The other was diffusely invaded by a metastatic grade 2 adenocarcinoma of the cylindroma type.

*Pathologic Aspects.*—Material for study consisted of tissue removed from the ear, from the preauricular and postauricular regions, and from the mastoid process (this last tissue had been removed prior to 1940). Available also was the metastatic nodule from the cervical region, removed on March 10, 1942. These specimens all had been preserved in formalin and were recut and re-studied from blocks of tissue treated by the fixed frozen section technique and stained routinely with hematoxylin and eosin. Stains for mucin also were employed.

(Fig. 1a and b). Under the higher power objectives of the microscope the tumor cells were seen to be small and deeply stained with hematoxylin. Size was remarkably uniform and cytoplasm was scanty in amount and ill defined in outline. The nuclei were relatively large, and very hyperchromatic, yet mitosis was rarely encountered. The cystic areas observed were seen to represent attempts at the formation of acini and alveoli, and the entire picture appeared to be compatible with a diagnosis of grade 1 adenocarcinoma (Broders), cylindroma type. Hyaline stromal changes so typical of cylindroma were noted.

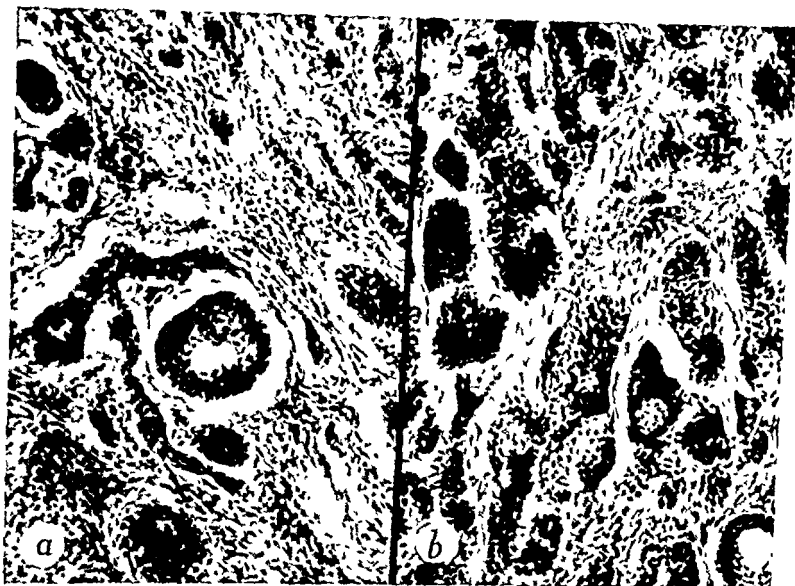


Fig. 1.—a, Primary lesion of the tongue, showing strands and solid and cystic cords of small hyperchromatic tumor cells (hematoxylin and eosin  $\times 135$ ); b, adenocarcinoma, grade 1, cylindroma type, from one of the metastatic nodules in the liver (hematoxylin and eosin  $\times 135$ ).

CASE 2.—A married white woman, 48 years old, first registered at the clinic on June 14, 1938, complaining of pain in the right ear, of nine years' duration. Her family history and past medical record had been irrelevant. The patient's husband and three children were living and well. Her present illness had begun nine years prior to registration, with intermittent pain in the region of the right ear. This pain continued, and when medical advice was sought a small tumor was discovered and removed. The pathologic report at that time was adenocarcinoma, probably of sebaceous glandular origin, and the patient was treated with a total of 5400 milligram hours of radium with a view to preventing recurrence. Temporary control was obtained, but pain returned.

Examination at the clinic disclosed what appeared to be a recurrence of a malignant process filling the right external auditory canal. Extension was apparent in the upper and inner aspect of the auricle. Postauricular tenderness was elicited. Roentgenograms of the right mastoid region revealed a diffuse cloudiness, with no actual evidence of destruction of bone.

At operation on June 15, 1938, an extensively recurrent neoplasm was found involving the entire external auditory meatus. The inner and upper surfaces of the auricle were involved and there was extension into the skin of the preauricular and postauricular regions. Deeply, involvement of the right mastoid process was apparent. An extensive operation, including mastoidectomy and removal of the vesicles,

was performed in an effort to eradicate the neoplastic tissue, which proved to be grade 2 adenocarcinoma of the cylindroma type. Postoperatively, intensive roentgen therapy was administered. The patient returned on four occasions for further observations and continuance of roentgen therapy. On her fourth admission (July 5, 1939), she complained of preauricular tenderness and a nodule in the mastoid region. Examination disclosed several zones of apparently recurrent neoplastic tissue in the preauricular and postauricular areas. These were treated by excision (cautery). Needles containing radium were inserted locally. Microscopically, the nodules of tissue removed again were typical of adenocarcinoma of the cylindroma type.

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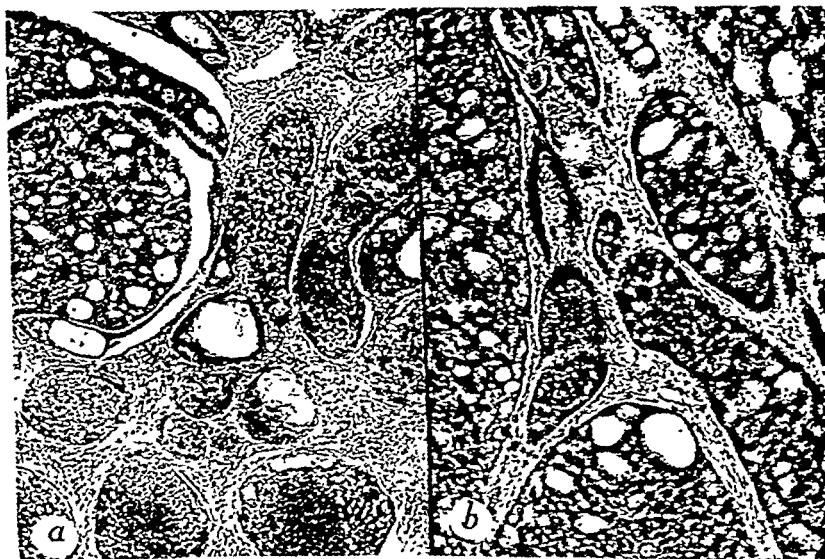


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Duplicating, for the most part, the picture described in connection with Case 1, certain variations were noted which merit special attention. Sections from the primary and the recurrent nodules appeared to be extremely cellular. Although in some areas the cylinders were small, in other zones they appeared very large and, indeed in some fields, a disposition in anastomosing sheets was apparent (Fig. 2a).

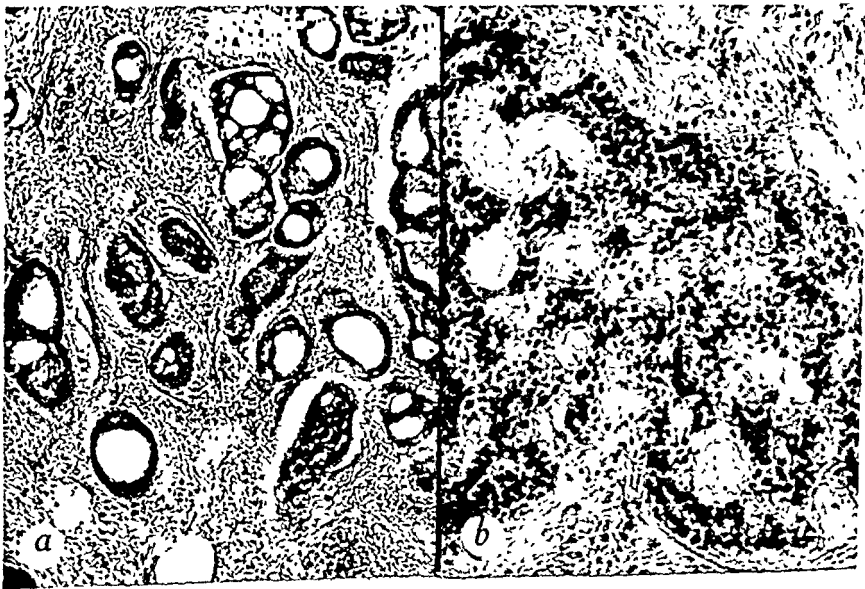


Fig. 3.—*a*, Section taken from the tissue removed for the thrombi of neoplastic cells are seen filling the lymphatic space (hematoxylin and eosin  $\times 60$ ); *b*, cores of the cylinders undergoing a process of necrosis (hematoxylin and eosin  $\times 200$ ).

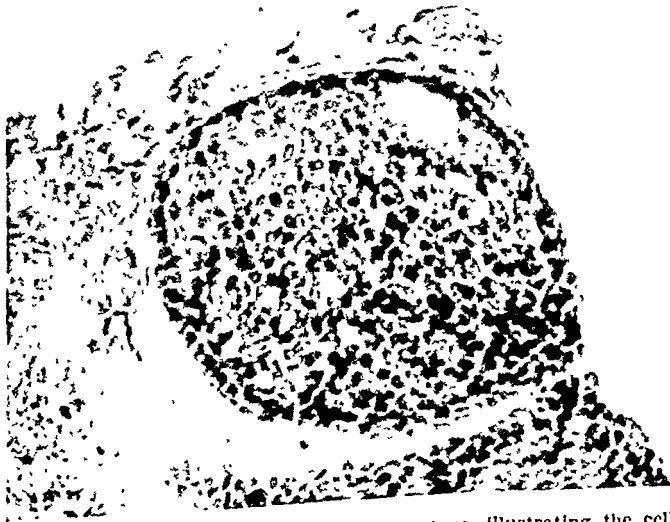


Fig. 4.—Adenocarcinoma, grade 2, cylindroma type, illustrating the cellularity of the neoplasm. The nuclei at the periphery of the cylinder appear in palisade (hematoxylin and eosin  $\times 300$ ).

Central "coring out" of the cylinders was extremely prominent, with a veritable honeycombing of entire fields. These "alveoli" varied considerably in size. Many of the cystic cores were empty; others were filled with a mucoid substance (Fig. 2*b*), and still others appeared to be undergoing a process of hyalinization. Under the high-power objective the general cytologic features of the cells appeared to be similar to those described for Case 1. However, in view of the greater variation in the size and shape of the cells and the finding of more than occasional mitoses, a diagnosis of grade 2 (low) adenocarcinoma, cylindroma type, seemed to fit the lesion best. No nerves were found in the sections, but thrombi of neoplastic cells were seen to have infiltrated all available lymphatic spaces (Fig. 3*a*). Special features of the metastatic nodule from the cervical region were a more pronounced tendency toward hyalinization (Fig. 3*b*) affecting both the "acini" and the stroma, and a degree of "palisading" (Fig. 4) not observed in the primary lesion. This palisading was most prominent at the peripheries of islands of tumor cells.

#### COMMENT

Adenocarcinoma of the cylindroma type is most frequently encountered in the parotid gland, where, according to Stein and Geschickter, the incidence is 17.4 per cent of the tumors arising therein. The submaxillary gland follows next in order, with approximately the same relative incidence of "cylindromas," but with a much smaller total number of neoplasms arising in this location. It is well known, however, that "cylindromas" can arise in connection with the lips, gums, tongue, floor and roof of the mouth, pharynx, larynx, and even the lacrimal gland. Briefly, they can occur wherever mucous glands are found about the head and neck.<sup>1</sup> The aforementioned locations are, in the same order of frequency, the favorable locations for the so-called mixed tumors. These characteristics, together with the fact that adenocarcinoma of the mixed tumor type is five to ten times more commonly encountered than adenocarcinoma of the cylindroma type, have combined to mask the distinction between these two forms of malignancy. The occasional discovery of neoplasms having features of both types has merely added to the difficulty. It has been our experience, however, that whenever a "mixed tumor" has exhibited cylindromatous areas microscopically, the prognosis has appeared to be almost as serious as it would be if the neoplasm existed as a pure "cylindroma."

Is the term "cylindroma" used ill advisedly in connection with neoplasms of this unusual type? Probably not, if the prefix *adenocarcinoma* is used to indicate an origin from glandular epithelium, so that confusion of the tumors with cylindromas of the skin is thereby avoided. This last mentioned type of neoplasm is a basal-cell epithelioma which is usually associated with a good prognosis.

The relatively long clinical history in each of these two cases of "cylindroma" is in keeping with our findings in connection with similar lesions of the submaxillary gland. It adds further to the difficulty of preoperative separation of the tumor from some of the more rapidly growing examples of mixed tumor. The persistent pain suffered by both patients recalls the frequency of pain (70 per cent) noted in our series

of submaxillary tumors. Finally, it is noteworthy that in both patients concerned in this report metastasis developed while the primary lesion seemingly was being controlled by local treatment. This observation emphasizes further not only the importance of the early recognition of "cylindromas" but also the necessity for a reserved, if not a guardedly bad, prognosis.

#### SUMMARY

Two examples of metastasizing adenocarcinomas of cylindroma type are recorded. These tumors can arise from many situations about the head and neck. They are sometimes confused with the more commonly occurring mixed tumors, but should be carefully delineated from the aforementioned group because "cylindromas" demand early treatment of a vigorously radical nature.

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## PROBLEMS IN THE SURGICAL MANAGEMENT OF DIABETIC GANGRENE

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THE surgical treatment of diabetic gangrene has presented a problem of increasing interest since the discovery and general use of insulin. Twenty years ago coma was the major complication and cause of death in diabetes mellitus. Relatively few patients with a severe form of the disease lived past midlife, and surgical deaths were proportionately infrequent. Joslin<sup>8</sup> found that 51 per cent of a series of 1,147 diabetic deaths prior to 1922 resulted from coma, while only 9.8 per cent could be attributed to surgical complications. At the present time coma is responsible for less than 5 per cent of the diabetic deaths. These patients now survive until the sixth or seventh decades, when heart disease or infection and gangrene of the lower extremities is the principal cause of death.

The purpose of this paper is to report our experience in the surgical management of diabetic gangrene at the University of Nebraska during the ten-year period from 1932 to 1942. The patients were all seen in the University Hospital, a teaching institution with 250 beds which accepts only charity patients from the entire state. This analysis covers a decade marked by prolonged drouth and repeated crop failures in this area. The majority of patients came to us from small rural communities, farms, and ranches. Many were first seen by their local physician when infection or gangrene of an extremity was well established and were immediately referred to the hospital for emergency surgery. It is obvious that problems encountered with such a group of patients will differ from those in private practice or even on a charity service in one of our large urban centers. Regular care or attendance at a medical clinic with supervision of the diet, insulin, and care of the extremities has not been the rule in those who were known to have diabetes. These factors must be kept in mind in considering the analysis of our results in the treatment of diabetic extremities with infection and gangrene.

From 1932 to 1942 admissions of patients with diabetes mellitus to the University Hospital were 802. Of these admissions, fifty-three diabetic patients with infection or gangrene of the lower extremities have been seen on the surgical service, an incidence of 6.6 per cent. John<sup>7</sup>



reported that the incidence of gangrene in diabetic patients varies from 2.4 to 18 per cent in the reported series; the average in thirteen large clinics is 5.2 per cent.

TABLE I  
SERIES OF FIFTY-THREE PATIENTS (1932-1942)

Males, 31 cases	Youngest	44 yr.
Females, 22 cases	Oldest	79 yr.
Average age:		
First five-year group (25 cases)		60 yr.
Second five-year group (28 cases)		61.5 yr.
Males		61 yr.
Females		60 yr.

The average age of these fifty-three patients was 61 years (Table I); the youngest was 44 years and the oldest, 79 years. Joslin<sup>9</sup> has shown, from figures of the Metropolitan Life Insurance Company, that since 1926 the average age of the diabetic patient at death has been increased from 44 to 61 years and that the average duration of the disease is from 4.8 to 9 years. Eliason<sup>5</sup> reported that the average age of patients with diabetic gangrene increased seven years between the years 1926 and 1933. In McKittrick's<sup>14</sup> recent review of 1,036 cases of diabetic gangrene, the average age was 65 years. McKittrick and Root<sup>11</sup> had previously found that in 60 per cent of their patients, diabetes developed after the age of 40 years and in only 25 per cent, between the ages of 25 and 40 years. The surgeon may therefore expect the diabetic patient with gangrene of an extremity to appear during the sixth decade of life.

In our group 32 per cent were considered to have mild diabetes on admission, 59 per cent, moderate to severe, and only 9 per cent, severe. This classification is only relative since the true metabolic status of the diabetic patient can only be evaluated when all infection is controlled. The fact remains, however, that the majority of patients in whom diabetic gangrene develops are not severe diabetics when their infection is eradicated and their carbohydrate metabolism stabilized.

One of the striking facts in this small series was the presence of definite gangrene in fifteen patients, or 28 per cent, before glycosuria was discovered (Table II). Twelve patients were admitted to the hos-

TABLE II  
KNOWN DURATION OF DIABETES IN SERIES OF FIFTY-THREE PATIENTS

TIME	CASES	PERCENTAGE
Unknown on admission	12	23
1 month to 1 yr.	5	9
1 to 2 yr.	4	8
2 to 5 yr.	11	21
5 to 10 yr.	11	21
Over 10 yr.	10	18

Fifteen patients, or 28 per cent, had gangrene before glycosuria was discovered.

pital before a diagnosis of diabetes was made, and twenty-one patients, or 40 per cent, had either not known they had diabetes when hospitalized or gave a history of glycosuria for less than two years. Eliason<sup>5</sup> found that 50 per cent of 175 patients with established diabetic gangrene admitted to the Philadelphia General Hospital were unaware that they had glycosuria.

Joslin<sup>9</sup> has aptly said that the surest way to produce gangrene in the diabetic patient is to keep him alive and provide inadequate treatment. This statement is amply supported by the infrequent occurrence of diabetic gangrene in patients under good medical supervision and the much higher incidence and mortality among the indigent. An example is the experience of Standard, Brandaleone, and Ralli<sup>20</sup> with diabetic gangrene in two series of patients. Prior to the onset of gangrene, one group had received adequate diabetic care, the other series none. In the latter series mortality from gangrene was twice as high and three times more frequent following major amputations as in the first group of previously treated patients.

The type of medical therapy received by our group of fifty-three patients prior to their admission with gangrene is listed in Table III.

TABLE III  
PREVIOUS TREATMENT FOR DIABETES IN SERIES OF FIFTY-THREE PATIENTS

TREATMENT	CASES	PERCENTAGE
None	21	39
Poor	11	21
Fair	17	32
Good	4	8

Of twenty-one patients untreated for their glycosuria, fifteen were admitted without knowledge that they had diabetes. A total of 60 per cent of patients known to have diabetes had received entirely inadequate treatment, while only 8 per cent had been under good medical management. Responsibility for this poor record in the medical control of these patients is difficult to assign. Economic conditions and distance from competent medical supervision were undoubtedly important factors. In addition, the ignorance and indifference of these individuals remain obstacles to be overcome. In those who had had previous hospitalization and instruction covering diet, use of insulin, and care of the extremities, this advice was often forgotten or ignored as soon as symptoms were relieved.

Education undoubtedly can and will help reduce the incidence of infection and gangrene in diabetic patients. The increasing popularity of periodic health examinations will bring to light many cases of mild diabetes which we may expect to develop during the fifth, sixth, and seventh decades. Simplified diets and the use of protamine insulin

are making adequate control easier for the diabetic patient of limited intelligence. Greater effort must be made to impress all diabetic patients with the importance of proper care of the feet.

In Table IV the known precipitating factors preceding the onset of gangrene in our series of patients are listed. Burns from hot water bottles, blisters from tight shoes, and the injudicious paring of corns were responsible, in the order named.

TABLE IV  
PRECIPITATING FACTORS PRECEDING ONSET OF GANGRENE

FACTORS	CASES	PERCENTAGE
Burns (hot water bottle)	8	14
Blisters (tight shoes)	5	9
Frostbite	2	4
Paring corns	4	8
Trauma	2	4
Unknown	32	61

Brandaleone<sup>1</sup> and his associates have emphasized the value of prophylactic foot care in patients with diabetes. They found in their series that special instruction in the care of the feet reduced the number of pedal infections requiring hospital admission from 10 to 4.6 per cent and the number of amputations, from 32.4 to 25.9 per cent.

Extensive wet gangrene of the toes and foot, often extending into the leg, was the most common type of lesion encountered (Table V).

TABLE V  
EXTENT OF PATHOLOGY ON ADMISSION IN SERIES OF FIFTY-THREE PATIENTS

PATHOLOGY	CASES	PERCENTAGE
Penetrating ulcers of feet	9	17
Dry gangrene (limited to toes)	6	11
Wet gangrene (toes—distal foot)	6	11
Extensive wet gangrene (foot)	32	61
Unilateral involvement	34	62
Bilateral involvement	19	38

These patients with toxemia, sepsis, acidosis, and uncontrollable diabetes and with the constant hazard of gas bacillus infection present a very grave surgical emergency. Those individuals with dry gangrene, infected penetrating ulcers of the feet, or moist gangrene limited to one or two toes were not acutely ill, and their treatment did not demand the same heroic measures. It is characteristic that nineteen patients, or 38 per cent of the group, had bilateral involvement of the lower extremities when first seen.

The relationship between arteriosclerosis and diabetes is now well appreciated. Experience has shown that the arteriosclerotic process continues to advance in spite of therapy, with the result that the diabetic patient's vessels are usually ten years older than the patient. Olmsted<sup>17</sup> has observed that pulsations in the lower extremities of

these patients tend to disappear ten to twenty years earlier than in nondiabetic individuals. Lisa, Magiday, and Hait<sup>10</sup> recently reported a study of the peripheral vessels in amputated gangrenous limbs of 106 patients. Of these, approximately one-half (fifty-five) were diabetic patients averaging 65 years of age, while the fifty-one with arteriosclerotic gangrene had an average of 68 years of age. In the vessels of the two groups of patients no characteristic pathologic differences could be distinguished.

Calcification of the peripheral vessels was demonstrated by x-ray by Morrison and Bogan<sup>16</sup> in 53 per cent of 324 consecutive diabetic patients and was demonstrable in 91 per cent of those who were known to have diabetes for a ten-year period. X-ray studies of the lower extremities of forty-three of our patients (Table VI) showed visible

TABLE VI

## X-RAY FINDINGS IN INVOLVED LIMBS IN SERIES OF FORTY-THREE PATIENTS

X-RAY FINDINGS	CASES	PERCENTAGE
No visible calcification	8	19
Moderate calcification	10	23
Marked calcification	16	37
Osteomyelitis, calcification	6	14
Gas in soft tissues	3	7

Ten patients not examined by x-ray.

calcification of the peripheral vessels in 74 per cent, with marked calcification in 37 per cent. Although a peripheral vessel demonstrating visible calcification cannot be assumed to be incapable of carrying blood, its ability to demonstrate palpable pulsations is important from the standpoint of prognosis and treatment. However, it is quite unusual to find either a pulsating dorsalis pedis or posterior tibial artery in an individual with marked calcification of the peripheral vessels. Gas in the soft tissues of the feet was noted by x-ray in three cases. This finding does not always indicate the presence of anaerobic gas-forming organisms since the colon group are capable of producing a similar picture. In two patients a diagnosis of gas bacillus infection was established by clinical and bacteriologic study, while in the third patient anaerobic organisms could not be demonstrated.

It is extremely difficult in a general hospital to standardize the treatment of any group of patients with diabetic gangrene. The problems presented by the individual case demand the closest possible cooperation between internist and surgeon. Experience in the majority of our large teaching clinics has amply demonstrated the importance of management of these patients by a small team of medical men and surgeons especially interested in these problems and equally willing to devote the required time and care. Every reported series of patients so handled has shown a striking improvement in mortality with a commendable reduction in hospital days. Our series of patients was not

thus supervised; the internist on service was responsible for the care of the diabetes and the surgeon on ward service at the time of the patient's admission was responsible for surgery. Inevitably this system will result in a higher mortality because of split responsibility, ultraconservatism of either internist or surgeon, and lack of the perfect teamwork essential in the management of these complex problems.

In the surgical treatment of patients with diabetic gangrene, the selection of the anesthetic agent is extremely important. The ideal anesthetic has a wide margin of safety, permits satisfactory performance of the proposed procedure, does not lower local tissue resistance, and interferes as little as possible with the patient's metabolism. Pentothal sodium has been our choice in minor surgical procedures, including amputation of toes, débridement, incision, and drainage. Low selective spinal anesthesia, using 50 mg. of novocain, has been very satisfactory for all major amputations. When an inhalation anesthetic was necessary, cyclopropane was preferred to nitrous oxide or nitrous oxide and ether. We have had no experience with anesthesia by reduced temperatures as recently advocated by Crossman and associates.<sup>2</sup>

For all procedures of election the patient is given his regular breakfast with necessary insulin at 7 A.M. After a period of three hours, surgery is carried out under pentothal or spinal anesthesia with little risk of nausea or vomiting. Two hours after operation orange juice is permitted by mouth and by evening the regular diabetic diet. Those admitted as surgical emergencies, requiring prompt débridement or open amputation, are given intravenous glucose covered with insulin to correct acidosis. Following operation they are given orange juice with necessary insulin at four-hour intervals; a diabetic diet is prescribed by the attending internist as soon as it can be tolerated.

TABLE VII  
TREATMENT IN SERIES OF FIFTY-THREE PATIENTS

TREATMENT	CASES	PER CENT	MORTALITY	
			CASES	PER CENT
Conservative therapy	17	32	2	12
Conservative surgery				
Incision and drainage	3	7	0	0
Toe amputation	7	13	0	0
Primary major amputation	19	35	7	37
Primary conservative surgery with subsequent major amputation	7	13	2	28
Major amputation requiring reamputation	2	4	1	50

There was a hospital mortality of 12 patients in series of 53, or 22.6 per cent.

There was an operative mortality of 10 patients in series of 36, or 27.7 per cent.

An outline of surgical treatment is given in Table VII. Conservative therapy with or without minor surgical procedures was used in twenty-seven patients, or 52 per cent of the series. In this group only two deaths occurred, both in patients admitted in extremis. It would be

ideal if all patients with infection or gangrene might be admitted sufficiently early to make conservative measures more frequently feasible, with resultant saving of limbs. Primary major amputation in nineteen patients resulted in seven deaths, a mortality rate of 37 per cent. In two patients major amputation required reamputation, with one death; and seven patients with primary conservative surgery were followed by subsequent major amputation, with two deaths. In this whole series of fifty-three patients, twelve died, a mortality of 22.6 per cent. Of the thirty-six patients operated upon, ten died, a surgical mortality of 27.7 per cent.

In an analysis of the mortality rate for major amputations in diabetic patients reported by sixteen surgeons, John<sup>7</sup> found a variation of from 5 to 65 per cent, depending upon the hospital and the type of patient. Williams and O'Kane<sup>21</sup> report that institution of a diabetic service reduced mortality from 85 to 36 per cent in a four-year period. Zierold's<sup>22</sup> mortality in major amputations dropped from 50 to 10 per cent in one year's time after institution of a two-stage procedure in the care of extensively infected patients. Pearse and Ziegler<sup>18</sup> record a similar decrease in mortality from 45 to 12 per cent. McKittrick<sup>14</sup> recently reported a commendable mortality rate of only 11.5 per cent in a series of 407 patients with diabetic gangrene subjected to a closed supracondylar amputation. This procedure, in the presence of extensive wet gangrene or infection, followed a previous open guillotine amputation below the knee.

The highest mortality in our group occurred in the nineteen cases of primary thigh amputation, a result to be anticipated in patients with extensive spreading infection, wet gangrene, and marked sepsis. Of this group, four succumbed to gas gangrene involving on admission the entire leg in two cases and arising in the amputation stump in the other two (Table VIII). Bilateral gangrene accounted for one death and sepsis and pneumonia for the remaining two fatalities.

TABLE VIII  
ANALYSIS OF CAUSE OF DEATH IN SERIES OF TWELVE PATIENTS

CAUSE OF DEATH	CASES	PERCENTAGE
Sepsis, arteriosclerosis, pneumonia	7	58
Gas bacillus infection		
Arising in amputation stump	2	17
Extensive involvement of limb	2	17
Toxemia, bilateral gangrene	1	8

For the last two years we have increasingly used a two-stage procedure in these desperately ill patients with wet gangrene, plantar space abscess, or spreading infection limited to the foot. Correction of ketosis is followed by extensive débridement of all infected and gangrenous tissue or wide incision, as suggested by Zierold.<sup>22</sup> Definite clinical improvement is usual, with return of normal temperature and

rapid relief from sepsis. After three days of normal temperature, a high amputation at the site of election is carried out in a patient whose general condition is greatly improved. McKittrick,<sup>13</sup> Pearse and Ziegler,<sup>18</sup> and also Gallie<sup>6</sup> advocate the employment of such a two-stage procedure but favor a guillotine amputation through the leg followed in a suitable period by a closed amputation at the supracondylar level. Our patients with infection and gangrene extending above the ankle have been treated by an open circular amputation in the mid-thigh with subsequent secondary closure.<sup>15</sup>

TABLE IX  
TYPES OF MAJOR AMPUTATIONS EMPLOYED

AMPUTATIONS EMPLOYED	CASES	PERCENTAGE
Circular midthigh drained	17	61
Circular midthigh not drained	4	14
Callander, no drain	4	14
Flap amputation below knee	3	11

There were twenty-eight major amputations in twenty-six patients.

A midthigh amputation with short anterior and posterior flaps was the most common procedure employed in this series of patients (Table IX). The type of amputation described by Callander was used four times; three patients had flap amputation below the knee, but this type of procedure has not been employed recently, and, in general, its use is not advisable in diabetic patients.<sup>3, 4, 11</sup> Anatomically the Callander amputation gives an excellent stump, but the considerably longer operative time required is often a distinct disadvantage. Our preference for the midthigh level has been dictated by the extent of pathology present and by the fact that such patients very rarely improve sufficiently to wear an artificial limb. The closed supracondylar amputation advocated by McKittrick<sup>13, 14</sup> and Samuels<sup>10</sup> is commendable in reducing time required for wound healing and the excellent stump which results. However, this type of closed procedure demands a clean operative field, meticulous technique, and previous control of any spreading infection in the adjacent leg.

Our experience with wound healing in these diabetic stumps confirms the dictum of Eliason that "clean wounds in diabetes do not heal as kindly as in nondiabetics."<sup>15</sup> He has reported that some form of infection with severe diffuse suppuration developed in 42 per cent of the amputation stumps in a large series of patients. In our series of 28 major amputations, definite wound infection developed in sixteen patients, or 57 per cent (Table X). Drainage for forty-eight hours was used in twenty patients, in twelve of which (60 per cent) frank wound infection developed. The wounds failed to heal by primary union or became infected in four of the remaining eight patients who had closed amputations. The controversy over use of drains after major amputations for diabetic gangrene is familiar to all interested in this type of

TABLE X

## WOUND HEALING IN SERIES OF TWENTY-EIGHT MAJOR AMPUTATIONS

	CASES	CLEAN WOUNDS		INFECTED WOUNDS	
		CASES	PER CENT	CASES	PER CENT
Circular mid thigh drained	17	6	35	11	65
Circular mid thigh not drained	4	1	25	3	75
Callander, no drain	4	3	75	1	25
Flap amputation below knee	3	2	66	1	33

surgery. In the majority of our series drains were deemed advisable because of the extensive adjacent infectious process, the frequency of gas infection, and the needed exit for serum. The trend of the past few years has definitely been toward nondrainage. Admittedly a drain may permit entrance of organisms into a clean wound and delay healing in tissue of low vitality, but if these amputation stumps are closed without drainage, any adjacent infection in the leg must be stabilized, hemostasis must be meticulous, and the possibility of a gas infection in the stump constantly kept in mind. The two-stage procedure in cases of extensive spreading infection, together with local use of sulfonamides, will undoubtedly reduce the number requiring drainage and will increase the number of clean wounds.

Diabetic gangrene is an extremely expensive disease, as proved by hospital records. Since the majority of these patients are aged and without funds, their care becomes the responsibility of charity or the taxpayer. The average number of hospital days for our entire series of 53 patients was 47.4 days; of those who survived, fifty-two days (Table XI). These figures agree with those of Eliason,<sup>5</sup> who reported

TABLE XI

## DAYS OF HOSPITALIZATION IN SERIES OF FIFTY-THREE PATIENTS

	DAYS
Average for entire group	47.4
Average for fatal cases	29
Average for nonfatal cases	52
Average for fatal operative cases before surgery	13.3
Average length life (fatal cases after surgery)	3

an average of 36.5 hospital days for his entire group of 170 patients and an average of 62.2 days for those who recovered.

Further analysis of our series discloses that those who succumbed following operation were in the hospital for an average of 13.3 days before surgery was undertaken. In certain cases it is thus apparent that entirely too long a period of conservative medical treatment intervened before surgical consultation was requested. The diabetic patient with wet gangrene or spreading infection will not and cannot respond to medical treatment until the infection is overcome by surgical means. Conservatism on the part of the medical attendant can be quite as disastrous as the same tendency in the consultant surgeon. The degree



of success attained in the management of patients with diabetic gangrene depends upon the close cooperation of a competent internist and surgeon, each accepting full responsibility for his part of the problem from the time of the patient's admission to the hospital.

Follow-up studies on any series of patients with diabetic gangrene are extremely discouraging. McKittrick and Pratt<sup>12</sup> found that only 33 per cent of 188 patients were alive two years after operation, and of these 34 per cent had had bilateral amputation. Eliason<sup>5</sup> reported that 55 per cent of his series of 175 patients were dead within one year after operation. Our follow-up on this series of patients, while incomplete, suggests similar results with approximately 50 per cent being dead within one year after their dismissal from the hospital. Few patients have recovered sufficiently to return to their former work or pursue any gainful occupation.

#### CONCLUSIONS

1. A group of fifty-three patients with diabetic gangrene occurring in a series of 802 patients admitted with diabetes is reviewed.

2. Adequate medical treatment of the diabetic patient and meticulous care of the extremities are the most important factors in reducing the incidence of diabetic gangrene.

3. Improved surgical results follow the more general appreciation of the underlying surgical principles governing the care of diabetic gangrene.

4. Close cooperation of an internist and surgeon familiar with these problems is essential if these critically ill patients are to receive adequate treatment.

5. Diabetic gangrene is an extremely expensive disease. The period of hospitalization is usually protracted, and few patients improve sufficiently to return to any gainful occupation.

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## STUDIES IN BACTERIOPHAGE

### VII. THE BEHAVIOR OF STAPHYLOCOCCUS BACTERIOPHAGE IN HUMAN SERUM AND BLOOD

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#### INTRODUCTION

MANY papers on staphylococcus bacteriophage have shown that the lytic activity is affected by such body fluids as blood, serum, and pus. Most of these studies are concerned with the power of serum to inhibit bacteriophage lysis. A review of this work has been reported in a previous communication.<sup>1</sup> We agree that nearly all normal human sera undiluted or in a 50 per cent dilution prevent bacteriophage lysis of bacteria in liquid medium in vitro. There is some effect, permanent or passing, with dilutions of 1 in 10 and 1 in 20, while higher dilutions are generally ineffective.<sup>2-9</sup> Repeated subcutaneous, intramuscular, and intravenous injections of bacteriophage into human beings or experimental animals may increase the phage-inhibiting power of their serum up to a level of complete phage inactivation. This anti-phage is either very much more potent than, or of an entirely different nature from, that found in normal individuals.

A few authors have shown that defibrinated or citrated blood also may inhibit staphylococcus-bacteriophage lysis.<sup>5, 6</sup>

On the basis of these findings, investigators have been led to believe that bacteriophage is inactivated within the body. However, observations on bacteriophage action in vivo do not fully support this idea. The recovery of bacteriophage from the body is difficult to explain on the basis of complete phage destruction by the blood or other body tissues. Potent staphylococcus phage has frequently been found in the exudate from a human lesion caused by staphylococci. We have isolated spontaneous staphylococcus phages from about 5 per cent of the cases of acute staphylococcus infections (furuncles and carbuncles) and whenever we have recovered bacteriophage from a lesion it has always been accompanied by a susceptible organism. According to Albee<sup>10</sup> the percentage of phage recovery may be much higher in chronic infections (osteomyelitis) and yet the lesions are usually filled with pus and tissue fluids. Two of our most potent polyvalent staphylococcus phages were isolated from the blood stream of patients suffering from staphylococcus septicemia, despite the fact that the blood of one such patient inhibited lysis by the recovered bacteriophage in liquid medium up to a dilution of 1 in 40.

It is true that bacteriophage injected intravenously either into normal patients or animals can only rarely be recovered from the blood after 24 hours. This is due in part to the excretion of phage in the urine, from which it can be recovered readily. However, the delay in the growth and the character of the colonies on blood agar plates when transplanted from broth blood cultures in cases of staphylococcus septicemia suggest the continued activity in the blood, 24 to 48 hours after intravenous injection. Furthermore, we have found that bacteriophage injected locally into furuncles and carbuncles may, in some cases, persist for a week and yet the serum of one such patient inhibited phage lysis in high dilutions in liquid as well as on solid media.<sup>1</sup>

It seemed to us to be worth-while to investigate these apparent inconsistencies. Therefore the studies presented herewith were planned.

#### EXPERIMENTAL TECHNIQUE

The blood and serum of fifteen individuals were repeatedly examined. Four of these were suffering from chronic furunculosis of several months' or years' duration. Ten, classified as normal, were completely well but two had had occasional staphylococcus infections in the past. One individual had received previously twelve subcutaneous injections of phage in an attempt to prevent recurrent boils, and had built up a strong phage-inhibiting factor in the serum (antiphage).

In the series to be presented, we studied 50, 66, and 100 per cent serum as well as undiluted, defibrinated, and heparinized blood. The serum dilutions represent the limits of the actual concentration of plasma in the blood.<sup>11</sup> Heparinized blood contained 750 units of heparin per cubic centimeter.<sup>12</sup> Citrated blood was not included in the experiments, previous work having shown that sodium citrate itself has a deleterious effect on bacteriophage.

Most of the experiments were set up either with 0.9 c.c. or 1.8 c.c. amounts of blood or serum undiluted or diluted in saline solution, and 0.1 c.c. of undiluted or diluted bacteriophage. A 5- to 6-hour-old *Staphylococcus aureus* culture in Savita, a yeast extract broth low in protein, diluted down to the fifth decimal dilution, was used in most of the experiments, in 0.1 c.c. amounts yielding about 100 to 500 colonies on the plate.

The titer of the phage was determined by counting plaques when the  $10^{-5}$  and  $10^{-6}$  dilutions were inoculated with approximately 250 million bacteria per cubic centimeter and 0.01 c.c. of each of these phage-bacteria mixtures was plated on a quadrant of a 1 per cent agar plate, which was then incubated overnight. An estimation of the lytic ability of the undiluted phage was made by inoculating a quadrant of an agar plate, first with 0.01 c.c. of a saline suspension of bacteria containing 250 million bacteria per cubic centimeter and then with 0.01 c.c. of the phage.

Staphylococcus-phage stock mixture  $S_1$  and bacterial strain D (a staphylococcus isolated from a case of septicemia) were used for the

most part. Many of the experiments were repeated with a pure strain of bacteriophage D'A and staphylococcus strain McA, also isolated from a case of septicemia.

All experiments were carried on for 1 week at 37° C. and at room temperature for the remainder of the experiment. Titrations were made at varying intervals, sometimes as early as 3 to 6 hours, and repeated after 24 and 96 hours, in some experiments also after 48 and 72 hours, always at 7 days, and often at longer intervals up to 4 weeks. Owing to the long duration of these experiments and the small quantities of blood which we were forced to use, it became necessary, usually at the time of the 7-day titration, to dilute the blood and the corresponding savita control with 1.0 c.c. of savita broth to compensate for evaporation.

### RESULTS

*The Behavior of Bacteriophage S<sub>1</sub> After Contact With 50 Per Cent, 66 Per cent, and Undiluted Human Serum and Heparinized and Defibrinated Blood in the Absence of Susceptible Bacteria.*—These experiments were conducted with two sera (B and C) from "normal" persons who had had an occasional staphylococcus infection and two sera (A and D) from patients suffering with chronic furunculosis. The effects on phage of the undiluted sera and the 50 and 66 per cent dilutions in saline were studied by titration of the bacteriophage on solid medium after contact for 3 hours, 24 hours, 96 hours, and 7 days with 0.1 c.c. of undiluted phage S<sub>1</sub> at 37° C.

At no time throughout the experiment did we find any significant difference between the sera from the normal persons and the sera from the chronically ill patients. All dilutions showed a progressive inhibiting effect upon phage, which was most marked within the first 24 hours and brought about complete or nearly complete destruction of all phage at the end of a 7-day period. The degree of inhibition depended directly upon the concentration of the serum.

Parallel experiments were then carried out with whole blood. Heparinized and defibrinated bloods O and M from "normal" individuals were used. Our results showed a very close similarity in the phage inhibitory effect of these two bloods. The effect was slightly below that of 66 per cent serum. Heparinized blood produced a slightly greater destruction than did defibrinated blood. The titer of phage in savita broth also fell during the 7-day period, the chief difference being the more rapid loss of titer of phage in contact with serum or blood in the first 24 hours. Composite curves are shown in Fig. 1; individual tests were practically identical.

*The Behavior of Bacteriophage in Savita Broth, in 66 Per Cent Serum, and in Heparinized and Defibrinated Blood in the Presence of Susceptible Bacteria.*—Whole defibrinated and heparinized blood and 66 per cent serum from patients O and M were studied in the presence and in the absence of bacteria. Fig. 2 shows the results obtained with

blood M. Neither 66 per cent serum nor whole blood produced any inhibition of bacteriophage in the presence of bacteria after 24 hours. There was actually an increase in the titer during this period. Between 24 and 96 hours the titer of phage remained the same, and then after 7 days a further increase occurred in the blood. This was slightly more pronounced in the presence of defibrinated blood than in heparinized blood or serum. In 66 per cent serum a very slight fall was observed. The results with blood O were similar except for the fact that in 24 hours there was a slight drop in titer. This increased after 96 hours of incubation, and increased still more after 7 days. In the savita control there was a fall in the titer of phage both with and without bacteria, although with bacteria there was an initial rise. There was the usual degree of phage inhibition of all three substances in the absence of bacteria.

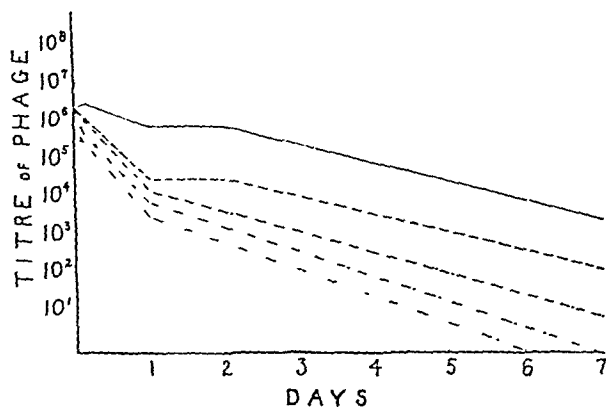


Fig. 1.—Effect of undiluted, 66 per cent, 50 per cent serum, whole defibrinated and heparinized blood on *Staphylococcus* bacteriophage in the absence of bacteria.

To study this phenomenon in greater detail we tested nine additional bloods. Of these, six were taken from normal individuals, two (S and K) from patients suffering with chronic furunculosis, and one (J) from an individual who had received twelve subcutaneous injections of phage in an effort to prevent recurrent furunculosis.

*Undiluted Phage.*—Fig. 3 shows the activity of undiluted phage S<sub>1</sub> containing approximately  $5 \times 10^5$  corpuseles per cubic centimeter in seven specimens of blood in the presence of bacteria. In 3 to 6 hours in each of the specimens there occurred a drop in titer. Then a sharp upward trend began, usually reaching the maximum titer in 24 to 48 hours. In 7 days, upon the addition of 1 c.c. of savita broth, to compensate for evaporation and the amounts taken for titration, a further increase in phage titer was observed in two of five which were so studied. In three a high level was maintained from the second to the fourth week. The savita control also showed a drop in titer during the first 3 to 6



most part. Many of the experiments were repeated with a pure strain of bacteriophage D'A and staphylococcus strain McA, also isolated from a case of septicemia.

All experiments were carried on for 1 week at 37° C. and at room temperature for the remainder of the experiment. Titrations were made at varying intervals, sometimes as early as 3 to 6 hours, and repeated after 24 and 96 hours, in some experiments also after 48 and 72 hours, always at 7 days, and often at longer intervals up to 4 weeks. Owing to the long duration of these experiments and the small quantities of blood which we were forced to use, it became necessary, usually at the time of the 7-day titration, to dilute the blood and the corresponding savita control with 1.0 c.c. of savita broth to compensate for evaporation.

### RESULTS

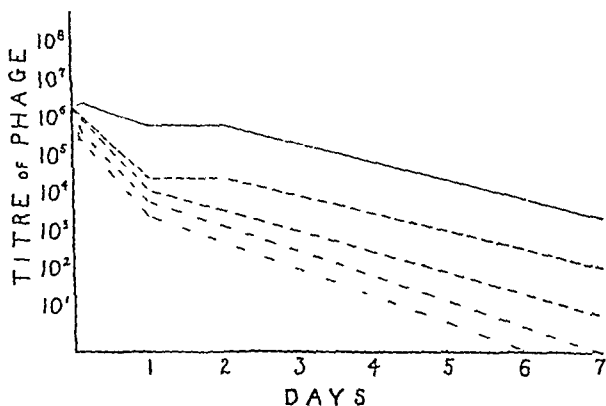
*The Behavior of Bacteriophage S<sub>1</sub> After Contact With 50 Per Cent, 66 Per cent, and Undiluted Human Serum and Heparinized and Defibrinated Blood in the Absence of Susceptible Bacteria.*—These experiments were conducted with two sera (B and C) from "normal" persons who had had an occasional staphylococcus infection and two sera (A and D) from patients suffering with chronic furunculosis. The effects on phage of the undiluted sera and the 50 and 66 per cent dilutions in saline were studied by titration of the bacteriophage on solid medium after contact for 3 hours, 24 hours, 96 hours, and 7 days with 0.1 c.c. of undiluted phage S, at 37° C.

At no time throughout the experiment did we find any significant difference between the sera from the normal persons and the sera from the chronically ill patients. All dilutions showed a progressive inhibiting effect upon phage, which was most marked within the first 24 hours and brought about complete or nearly complete destruction of all phage at the end of a 7-day period. The degree of inhibition depended directly upon the concentration of the serum.

Parallel experiments were then carried out with whole blood. Heparinized and defibrinated bloods O and M from "normal" individuals were used. Our results showed a very close similarity in the phage inhibitory effect of these two bloods. The effect was slightly below that of 66 per cent serum. Heparinized blood produced a slightly greater destruction than did defibrinated blood. The titer of phage in savita broth also fell during the 7-day period, the chief difference being the more rapid loss of titer of phage in contact with serum or blood in the first 24 hours. Composite curves are shown in Fig. 1; individual tests were practically identical.

*The Behavior of Bacteriophage in Savita Broth, in 66 Per Cent Serum, and in Heparinized and Defibrinated Blood in the Presence of Susceptible Bacteria.*—Whole defibrinated and heparinized blood and 66 per cent serum from patients O and M were studied in the presence and in the absence of bacteria. Fig. 2 shows the results obtained with

blood M. Neither 66 per cent serum nor whole blood produced any inhibition of bacteriophage in the presence of bacteria after 24 hours. There was actually an increase in the titer during this period. Between 24 and 96 hours the titer of phage remained the same, and then after 7 days a further increase occurred in the blood. This was slightly more pronounced in the presence of defibrinated blood than in heparinized blood or serum. In 66 per cent serum a very slight fall was observed. The results with blood O were similar except for the fact that in 24 hours there was a slight drop in titer. This increased after 96 hours of incubation, and increased still more after 7 days. In the savita control there was a fall in the titer of phage both with and without bacteria, although with bacteria there was an initial rise. There was the usual degree of phage inhibition of all three substances in the absence of bacteria.



- Titer of phage control in savita broth  
 -- Titer of phage in 50 per cent serum  
 - - - Titer of phage in whole defibrinated blood  
 - - - Titer of phage in whole heparinized blood  
 ... Titer of phage in 66 per cent serum  
 ... Titer of phage in undiluted serum

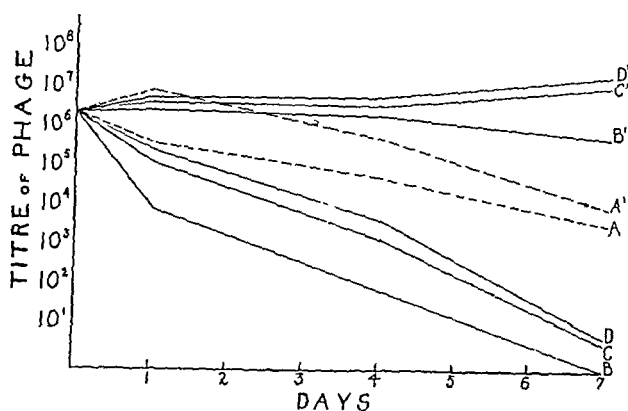
Fig. 1.—Effect of undiluted, 66 per cent, 50 per cent serum, whole defibrinated and heparinized blood on *Staphylococcus* bacteriophage in the absence of bacteria.

To study this phenomenon in greater detail we tested nine additional bloods. Of these, six were taken from normal individuals, two (S and K) from patients suffering with chronic furunculosis, and one (J) from an individual who had received twelve subcutaneous injections of phage in an effort to prevent recurrent furunculosis.

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hour period and an increase in 24 hours. Upon further incubation there was a definite downward trend which continued and was slightly or in no way affected by the addition of 1 c.c. of fresh savita on the seventh day.

*Phage Diluted 100 and 1000 Times.*—Fig. 4 shows the activity of a  $10^{-2}$  dilution of phage,  $S_1$ , in the presence of bacteria in nine specimens



- A. Phage in savita  
B. Phage in 66 per cent serum  
C. Phage in heparinized blood  
D. Phage in defibrinated blood

- A'. Phage in savita with bacteria  
B'. Phage in 66 per cent serum with bacteria  
C'. Phage in heparinized blood with bacteria  
D'. Phage in defibrinated blood with bacteria

Fig. 2.—The effect of 66 per cent serum M, whole defibrinated and heparinized blood M on *Staphylococcus* phage  $S_1$  after 24 hours, 96 hours, and 7 days' incubation in the presence and absence of fifty susceptible organisms per cubic centimeter

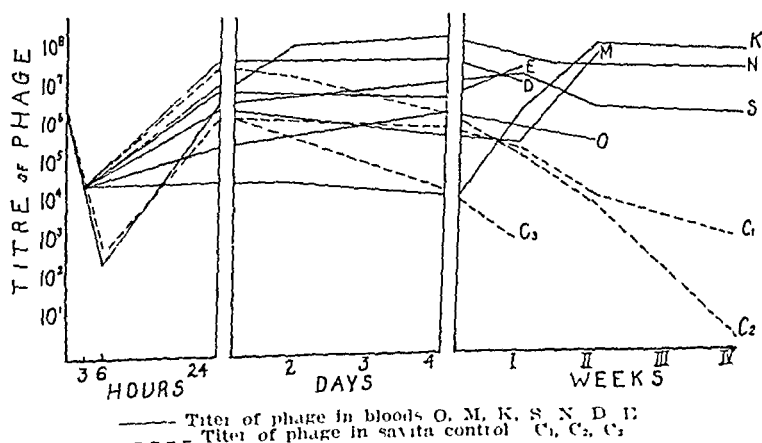


Fig. 3.—Titer of undiluted *Staphylococcus* phage  $S_1$  propagated in defibrinated bloods O, M, K, S, N, D, E in the presence of susceptible bacteria

of blood. Four of these bloods are the same as those used with undiluted phage. From this chart we can see that in all cases there occurred an initial drop in phage titer between 3 to 6 hours.

In 24 hours a considerable amount of individual variation in phage activity in different bloods can be seen clearly. In four specimens of

blood there was a definite multiplication of bacteriophage. In one of these four bloods the phage reached the original titer, that is, it multiplied 1000 times in 24 hours. In four other bloods the titer continued to rise after 24 hours. When 1 c.c. of savita was added to the tubes on the seventh day of incubation the titer often continued to increase. In those cases which reached a high titer the bacteriophage maintained this level for at least 4 weeks, the duration of the experiment. In three bloods a gradual decrease of the phage titer occurred so that within 1 week all traces of phage had disappeared and the addition of savita on the seventh day failed to revive them.

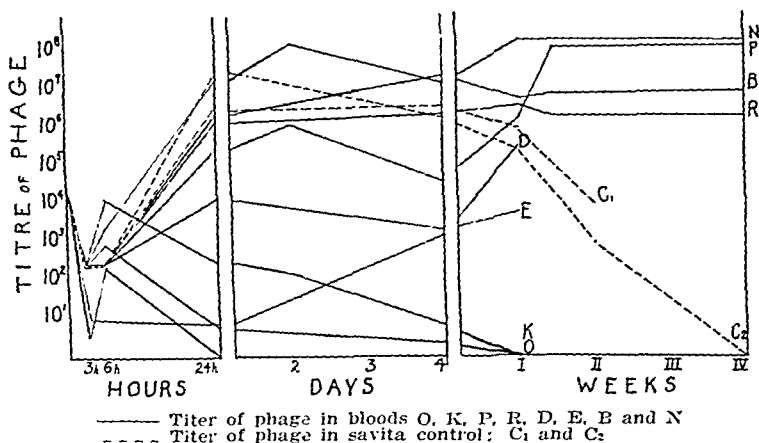


Fig. 4.—Titer of  $10^{-2}$  dilution of *Staphylococcus* phage  $S_1$  propagated in defibrinated bloods O, K, P, R, D, E, B and N in the presence of bacteria.

In one blood (E) the bacteriophage seems not to have multiplied at all, but it did not disappear upon incubation.

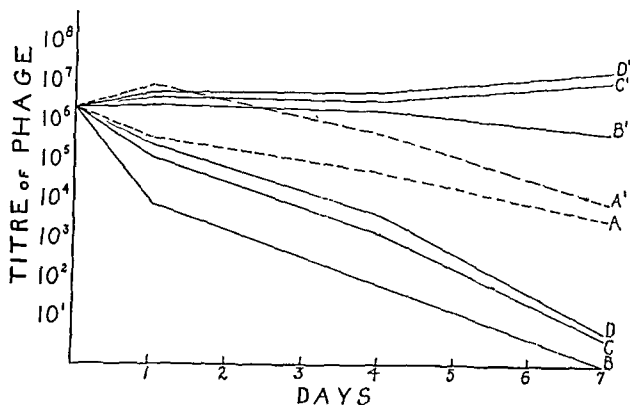
The corresponding control of  $10^{-2}$  dilution of phage in savita reached its maximum titer within 24 hours. After this time the titer steadily decreased and phage disappeared in spite of the addition of a fresh savita inoculum on the seventh day.

Bacteriophage  $S_1$  in a dilution of  $10^{-4}$  was propagated at the expense of a small number of bacteria in five specimens of blood. In four of these specimens all evidence of phage disappeared in 3 to 48 hours. Only in one blood was there a definite indication of bacteriophage multiplication. The phage controls in savita behaved similarly to those in a dilution of  $10^{-2}$ .

*Effect of Undiluted Blood on Bacteriophage in the Presence of Different Amounts of Bacteria.*—In this experiment a series of four tubes with 0.9 c.c. of heparinized blood plus 0.1 c.c. of phage were inoculated with 100, with 10,000, with 1,000,000, and with 200,000,000 bacteria respectively, all being suspended in 0.1 c.c. of savita. Four tubes of savita broth plus phage suspensions were inoculated with bacteria in a similar way as controls.

hour period and an increase in 24 hours. Upon further incubation there was a definite downward trend which continued and was slightly or in no way affected by the addition of 1 c.c. of fresh savita on the seventh day.

*Phage Diluted 100 and 1000 Times.*—Fig. 4 shows the activity of a  $10^{-2}$  dilution of phage,  $S_1$ , in the presence of bacteria in nine specimens



- A. Phage in savita  
B. Phage in 66 per cent serum  
C. Phage in heparinized blood  
D. Phage in defibrinated blood

- A'. Phage in savita with bacteria  
B'. Phage in 66 per cent serum with bacteria  
C'. Phage in heparinized blood with bacteria  
D'. Phage in defibrinated blood with bacteria

Fig. 2.—The effect of 66 per cent serum M, whole defibrinated and heparinized blood M on *Staphylococcus* phage  $S_1$  after 24 hours, 96 hours, and 7 days' incubation in the presence and absence of fifty susceptible organisms per cubic centimeter.

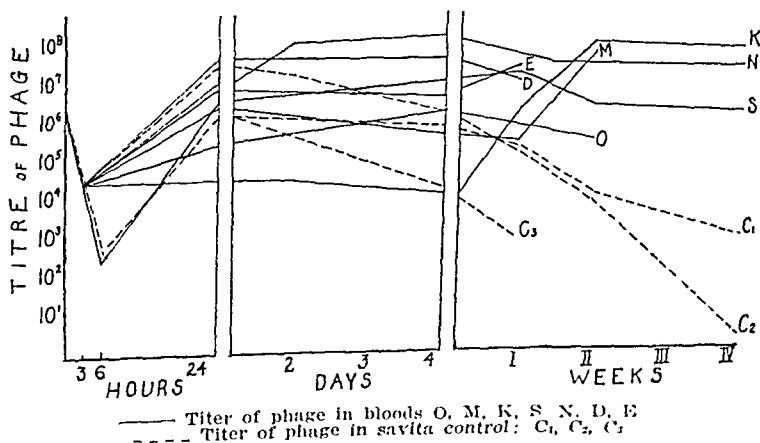


Fig. 3.—Titer of undiluted *Staphylococcus* phage  $S_1$  propagated in defibrinated bloods O, M, K, S, N, D, E in the presence of susceptible bacteria.

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In 24 hours a considerable amount of individual variation in phage activity in different bloods can be seen clearly. In four specimens of

before there can be any time for the development of immunity and before any antibacterial substances can be demonstrated. With regard to bacterial dissociation the question arises whether dissociation can take place without associated bacterial lysis. This factor cannot be ruled out. Increased leucocytosis and phagocytosis may take place but this is not a striking feature of patients who recover, nor is a falling leucocytic count indicative of a bad prognosis.

The studies presented above indicate that the possibility of bacterial lysis and propagation of bacteriophages in vivo must be given further consideration. We have obtained potent spontaneous bacteriophages from the blood of patients with staphylococcus septicemia before the injection of our stock bacteriophage. We have obtained phage from the urine after intravenous injection. We have occasionally found phage in pus, which yielded no bacterial growth, 24 hours after local instillation of stock phage into local lesions. These observations in addition to the above data would seem to support the belief that phage may at times propagate and produce lysis in vivo.

There is evidence that every specimen of human blood is capable of destroying a certain number of bacteriophage corpuscles. Knowing that 0.1 c.c. of  $10^{-4}$  dilution of phage in 0.9 c.c. of blood contains approximately five times  $10^{-4}$  bacteriophage corpuscles we can conclude that many bloods are capable of destroying this number of phage corpuscles; some bloods seem capable of destroying an even higher number.

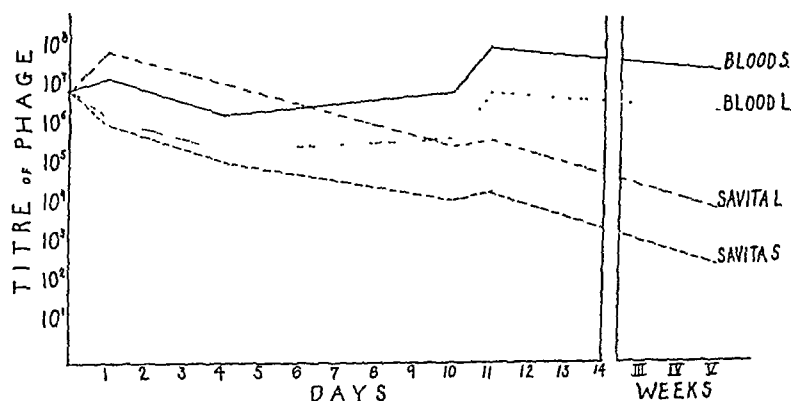
The clearest picture of the effect of blood on phage is obtained with the  $10^{-2}$  dilution because it brings out the difference between the inhibiting power of different bloods. This test might be used to indicate which bloods will permit and which will prevent the multiplication of phage, and in what cases very large doses of phage are indicated therapeutically.

In contrast to this, when undiluted phage is used the number of phage corpuscles which survive are able to propagate in every specimen of blood. This suggests that provided a sufficiently large amount of potent bacteriophage is injected intravenously, there will be a certain number of corpuscles which will escape any deleterious effect of blood and will begin to multiply. The same should hold true in cases of local lesions caused by staphylococci.

In the presence of blood or serum the optimum ratio for lysis of phage corpuscles to bacterial cells may change because the blood or serum may either favor or retard the growth of the bacteria or favor or retard the lytic action of the phage.

The deterioration of bacteriophage in vitro is a phenomenon of considerable practical importance. Not until some way is found invariably to develop potent phages and to maintain the potency over a long period of time can we expect effective phages to be prepared commercially and used extensively. Researches in this direction are being carried on and will be reported in subsequent papers.

Titration were carried out at varying periods of time from 24 hours to 25 days of incubation. The blood containing 100 bacteria per cubic centimeter gave a higher count than that which contained a greater number of bacteria. On the other hand, the titer of phage propagated in savita was the highest when propagated at the expense of 200 million bacteria and lowest in the presence of an inoculum of 100 bacteria per cubic centimeter. Fig. 5 shows the titer of phage  $S_1$  propagated in blood and savita at the expense of 100 bacteria and 200 million bacteria per cubic centimeter respectively. These experiments were repeated with the same result with other specimens of heparinized and defibrinated blood.



— Blood S. No. = 100 bacteria per c.c.  
 ... Blood L. No. = 200 million bacteria per c.c.

--- Savita S. No. = 100 bacteria per c.c.  
 -.- Savita L. No. = 200 million bacteria per c.c.

Fig. 5.—Effect of whole blood on Staphylococcus phage in the presence of different amounts of bacteria.

#### DISCUSSION

Most workers in the field of bacteriophagy accept the reported observations that blood inactivates phage or prevents its lytic action and have assumed, therefore, that the clinical benefit seen following bacteriophage therapy in cases of bacterial infection cannot be due to bacterial lysis *in vivo*. Such an opinion is expressed by Krueger and Seribmer in their recent review of the bacteriophage problem.<sup>13</sup> They state this rather emphatically and say that if bacteriophage is of any benefit in such cases the explanation will have to be found in one or more of the other possibilities, namely (1) increased leucocytosis and phagocytosis, (2) bacterial dissociation with avirulent progeny, (3) the stimulation of antibacterial immunity of a specific or nonspecific nature or (4) protein shock.

Our experience with bacteriophage in the treatment of staphylococcus septicemia would seem to cast doubt upon items (4) and (3) because we have propagated our phage in savita medium, which is practically protein-free, and we seldom see any reaction indicative of protein shock. Furthermore, the clinical benefit is often apparent in 24 to 48 hours

5. Phages propagated in the blood at the expense of 100 bacteria per cubic centimeter reached a higher titer than did phages propagated in the blood at the expense of 200 million bacteria. This was contrary to the behavior of phage when propagated in savita.

6. When  $10^{-4}$  dilutions of phage containing an average of  $5 \times 10^4$  corpuscles per cubic centimeter were incubated in blood in the presence of susceptible bacteria, a complete inactivation of phage within 3 to 48 hours took place in most of the tested bloods.

7. Thus, the survival and lytic power of phage in blood probably depends to a considerable degree on the concentration of phage corpuscles. If this number exceeds the amount which the blood can destroy, multiplication of phage in the blood may subsequently take place.

8. The use of staphylococcus phage in dilution  $10^{-2}$  containing an average of  $5 \times 10^6$  corpuscles in blood in the presence of susceptible bacteria makes it possible to distinguish between those bloods which will and those which will not allow the multiplication of phage corpuscles.

9. On the basis of these experiments we believe that multiplication of phage takes place in blood and other body fluids in vivo provided that a sufficiently large amount of potent phage is used.

We wish to express our appreciation for the technical assistance of Miss Catherine Capraro and Miss Olga Mordvin.

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It must be constantly borne in mind that the action of bacteriophage in vitro differs from that in vivo. In the latter the blood is constantly renewed and the pH maintained and the blood stream has an extremely strong bactericidal action both in the blood elements and the phagocytic power of the capillary and cellulum. Blood cultures suggest that the number of viable organisms is usually less than 200 per cubic centimeter. In vitro the blood is not renewed; the cells die and the phagocytic power is gradually lost, and there is less inhibition of the growth of the organisms.

If doses of bacteriophage are given in amounts ranging from 50 to 100 c.c. a day, the dilution in the body becomes approximately 1 to 100. With viable bacteria in the blood stream ranging from 20 to 500 organisms per cubic centimeter, our experiments suggest that the propagation of phage and the lysis of bacteria in vivo are well within the range of possibility. Our experiments also suggest that bacteriophage should be given in as large quantities as possible in order to favor this function. Furthermore, it should be given daily in divided doses until a favorable result is obtained as indicated by the disappearance of a positive blood culture. Further studies will have to be made in order to find out why certain bloods inhibit bacteriophage and an effort made to prevent this inhibition. In all studies of bacteriophage, emphasis should be placed upon the potency of the phage. It should be clearly stated whether the criterion of potency is the clearing of the culture in fluid medium or the complete inhibition of bacterial growth as indicated by the absence of colonies when the cleared culture is transferred to the blood agar plate—double potency test.<sup>17</sup>

#### SUMMARY

1. All specimens of human blood brought into contact with undiluted staphylococcus phage containing an average of  $5 \times 10^6$  virgules per cubic centimeter in the absence of bacteria produced a gradual inactivation of the phage, which was most marked within the first 24 hours and after 7 to 14 days all of the phage was usually destroyed.

2. Human serum produced a similar phage-inactivating effect, the degree of inactivation depending on the concentration of serum; undiluted and 66 per cent serum possessed a higher phage-inhibiting effect than whole defibrinated or heparinized blood, and 50 per cent serum had a slightly lower effect.

3. There was no significant difference in the phage-inhibiting effect between the blood or serum of individuals suffering from chronic furunculosis and the blood or serum of normal people.

4. When staphylococcus phage suspensions containing  $5 \times 10^6$  virgules per cubic centimeter were incubated in whole blood in the presence of susceptible bacteria, bacteriophage was never completely inactivated by any of the bloods tested, and multiplication of phage occurred within 24 hours in most of the bloods.

Physical examination at the time of the patient's admission to the hospital showed that she was well developed and well nourished. She was suffering rather severe pain. The temperature was normal, the pulse rate was 84, and the blood pressure was 174 systolic and 108 diastolic. The heart was of normal size, but a blowing systolic murmur was heard over the entire precordium. There was generalized tenderness over the abdomen, with the maximum tenderness in the right upper quadrant, just below the costal margin. The white blood cell count was 27,700, with 73 per cent polymorphonuclears, 5 per cent staff forms, 8 per cent lymphocytes, and 14 per cent monocytes. The blood cholesterol value was 147 mg. per hundred cubic centimeters, and the icteric index was 6.9. Twelve hours after admission the white blood cell count was 29,000.

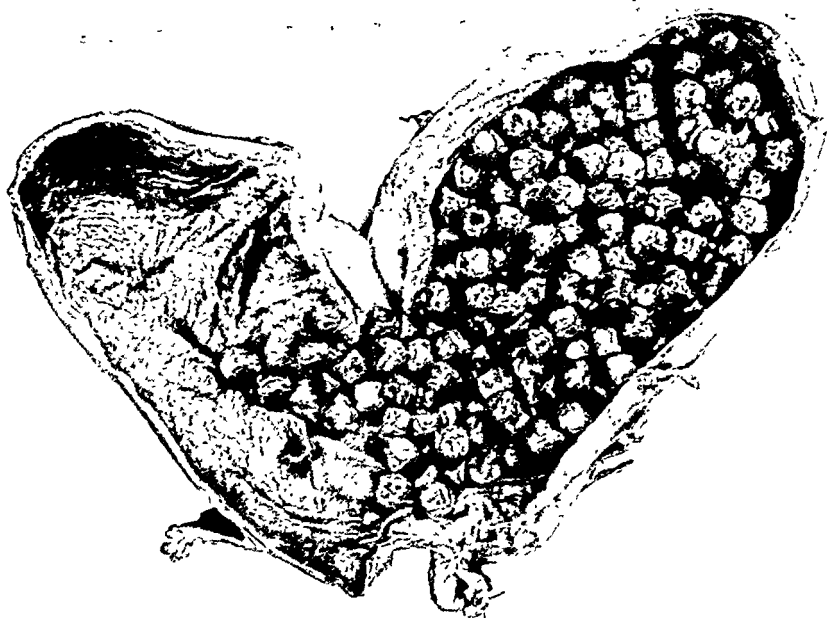


Fig. 1.—Gross specimen of infarction of the gall bladder.

A clinical diagnosis of acute cholecystitis was made, and on March 27 cholecystectomy was done. The abdomen was opened by a right rectus incision, and an enormously distended gall bladder was immediately presented. For the most part it was a blackish brown, and at one point a small tag of omental tissue was lightly adherent. The gall bladder was quickly removed from the fundus downward, the cystic duct and the cystic vessels being ligated separately. The wound was closed in layers around a cigarette drain.

The postoperative course was satisfactory, except for a persistently rapid pulse rate, until March 30, the third postoperative day, when the patient began suddenly to complain of palpitation and clammy perspiration. Examination revealed a grossly irregular cardiac rhythm, with the apical rate 120 to 160 and the radial rate 90 to 100, a pulse deficit of 20 to 60. An electrocardiogram made at this time was characteristic of auricular fibrillation with a rate of 250. Treatment with digitalis was started immediately but was discontinued after several hours because of the advent of ventricular extrasystoles. Quinidine was given, and the pulse became regular, but this medication also had to be stopped, in this case be-

## INFARCTION OF THE GALL BLADDER

FREDERICK CHRISTOPHER,\* M.D., E. L. BENJAMIN,† M.D., AND  
F. K. GOWDY, M.D., WINNETKA, ILL.

**G**ANGRENE of the gall bladder without infection and due to infarction is uncommon. In 1929 Vest<sup>1</sup> reviewed eighty cases of gangrene of the gall bladder, not including the sixty cases reviewed by Baumgartner<sup>2</sup> of the Mayo Clinic. Vest listed the following causes of gangrene of the gall bladder: (1) infection; (2) edema of structures adjacent to the cystic vessels; (3) stones plus infection and pressure; (4) mechanical factors, including (a) torsion, (b) angulation of the cystic duct by distention, (c) glands or tumors, (d) embolism or thrombosis of the cystic ducts (no proved case) and (e) distention spasm. Mark<sup>3</sup> reported four cases of gall bladder infarction. In two of these there was arterial change, and in two there was venous thrombosis. Mark described five varieties of vascular disturbances and said he believed that arteriosclerosis is an etiologic factor.

As Judd and Waldron<sup>4</sup> have pointed out, there is no accurate guide to the diagnosis of gangrene of the gall bladder. There may be marked tenderness and rigidity in the right upper quadrant, but the symptoms may be mild.

### CASE REPORT

A widow, 59 years of age, was admitted to the Evanston Hospital on March 26, 1942. For thirty-two hours she had suffered from continuous pain in the right upper quadrant. Several hours after the onset of the pain she began to have nausea and vomiting.

The past history was not significant except for the preceding six weeks, during which time she was under treatment by an osteopath for "sciatica" and multiple joint pains. Large doses of empirin compound were taken during that period. Before entrance to the hospital the patient was seen twice at her home, the first time being twelve hours after the onset of generalized abdominal discomfort with slowly increasing nausea. The temperature was 98.4° F., the pulse rate was 86, and the blood pressure was 176 systolic and 108 diastolic. Examination showed moderate generalized abdominal tenderness and a nodular tender mass the size of an orange in the lateral portion of the right upper quadrant just below the costal margin. Noted also was a patchy vesiculopapular eruption on the palms and a papular purpuric eruption on the inner aspects of the soles, these lesions having started four or five weeks before. Six hours later all the symptoms were increased, vomiting of bile had occurred twice, the temperature was 99° F., and the mass was slightly larger, smoother, and more tender. The clinical diagnosis was inflammatory tumor of the right upper quadrant of uncertain origin, hypertension, possibly transient, and dermatitis medicamentosa from empirin compound. Hospitalization was advised for surgical treatment.

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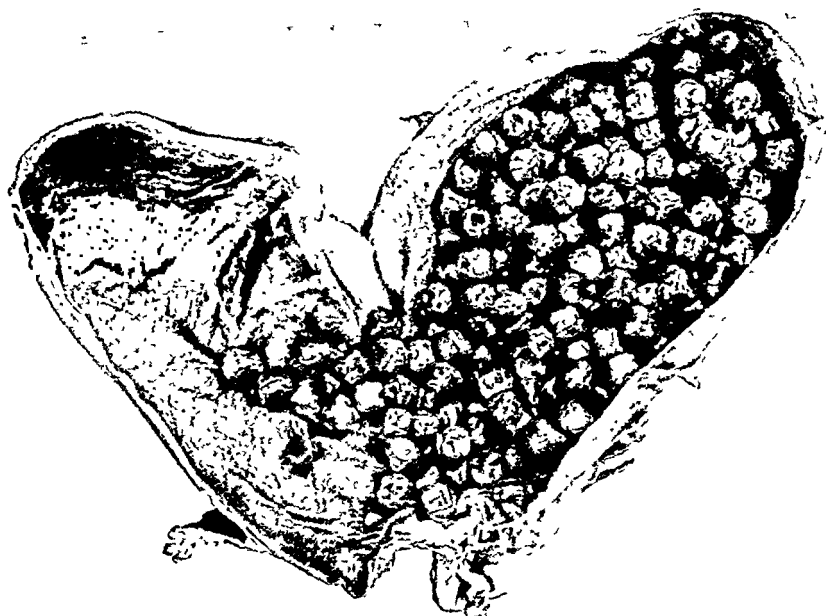


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cause of nausea. However, fibrillation did not recur. An electrocardiogram made on April 2 revealed sinus mechanism interrupted occasionally by ectopic nodal and ventricular beats. The convalescence was uneventful from that time on, and the patient was discharged from the hospital on April 12, the sixteenth postoperative day. The subsequent course has been satisfactory.

The report on the pathologic specimen was as follows:

*Gross Description.*—The gall bladder was huge, weighing 580 Gm. and measuring 16 cm. in length. Twenty-one millimeters of cystic duct were attached. The external circumferences were as follows: corpus, 26 cm.; fundus, 25.5 cm.; and neck, 12 cm. The hepatic surface measured 12 by 8 cm. Most of the free serosal surface was smooth and light to dark red, but the corpus and neck were covered with an oblique strand of fatty adhesions attached for a distance of 11 cm. and measuring 3 cm. in length. The lumen contained 200 ml. of dark green bile, 300 (by actual count) faceted cholesterol stones up to 12 mm. in diameter, and myriads of smaller concretions 1 to 2 mm. in diameter. The dark red wall varied in width from 3 to 10 mm. The serosa and mucosa separated spontaneously when the gall bladder was opened. The dark green mucosa was smooth except for several submucosal linear strands. No infection or ulceration was noted.

*Microscopic Description.*—The various sections showed practically no viable structures. The wall was converted into a swollen, pale pink, ghostlike structure with linear zones of polymorphonuclear leucocytes beneath the serosa. There was extensive erythrocytic extravasation throughout. There was no involvement of the cystic artery. The cause of the infarction could not be determined from examination of the specimen.

*Diagnosis.*—Hemorrhagic infarction of the gall bladder; cholecystolithiasis.

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# FAILURE TO RECOVER SULFONAMIDES FROM GALL BLADDER BILE IN DOGS WITH CYSTIC DUCT OBSTRUCTION

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IT HAS been demonstrated that sulfonamides are excreted in the bile in man and in certain laboratory animals,<sup>1, 4, 6, 8, 9</sup> and there is clinical evidence that these drugs exert a beneficial effect in some biliary tract infections.<sup>1, 4, 5, 8</sup> On the other hand, in many cases of biliary tract disease there is no benefit from the drugs, and, as Watson and Spink<sup>10, 11</sup> have shown, hepatic injury actually may be produced, particularly after the administration of sulfanilamide. In our clinic, observation of several patients with acute obstructive cholecystitis has indicated that the administration of sulfonamides in such cases does not alter the course of the disease. Therefore, it is desirable to learn whether obstruction of the cystic duct prevents these drugs from entering the gall bladder, or whether they can reach the gall bladder bile through the vesical wall. This study was undertaken to secure information regarding that question.

## METHOD OF EXPERIMENTATION

The experiments were carried out upon twelve healthy adult dogs. Under ether anesthesia and with aseptic surgical technique the cystic duct was isolated and ligated without injury to the blood supply of the gall bladder. The following day, when the animal had recovered from the operation, one of the sulfonamide drugs was administered by mouth (sulfanilamide, sulfathiazole, and sulfadiazine were used). In some cases the drug was administered in a single dose, in other instances in divided doses (see Tables I and II). The animal was sacrificed later,

TABLE I

DOG NO.	WEIGHT (KG.)	DRUG	DOSE*	SULFONAMIDE IN GALL BLADDER BILE	GROSS APPEARANCE OF GALL BLADDER	MICROSCOPIC APPEARANCE OF GALL BLADDER
111	11	Sulfanilamide	1 dose 8 Gm.	None	Normal	Normal
115	13	Sulfathiazole	1 dose 8 Gm.	None	Normal	Normal
117	16	Sulfadiazine	1 dose 8 Gm.	None	Normal	Normal

\*Sacrificed seven hours after drug was administered.

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TABLE II

DOG NO.	WEIGHT (KG.)	DRUG	DOSE	GALL BLADDER ANALYSIS	VENOUS BLOOD ANALYSIS (MG. % FREE SULFONAMIDE)	GROSS APPEARANCE OF GALL BLADDER	MICROSCOPIC APPEARANCE OF GALL BLADDER
126	6	Sulfanilamide	1 dose 4 Gm., 4 hr. later	No sulfanilamide	45.9	Normal	Normal
128	6	Sulfathiazole	1 dose 40 gr., 4 hr. later	No sulfathiazole	9.1	Normal	Normal
132	7	Sulfadiazine	2 doses of 5 Gm. each, sacrificed 6 hr. later	No sulfadiazine	10	Normal	Normal
133	6	Sulfathiazole	As above	No sulfathiazole	10	Normal	Normal
134	5	Sulfanilamide	As above	No sulfanilamide	45	Normal	Normal
135	8	Sulfanilamide	As above	No sulfanilamide	62	Normal	Normal
136	18	Sulfanilamide	2 Gm. b.i.d. x 2 days, 2 Gm. 4 hr. before sacrifice	No sulfanilamide	15.8	Normal	Normal
137	16	Sulfanilamide	As above	No sulfanilamide	18.2	Normal	Normal
138	18	Sulfanilamide	As above	No sulfanilamide	15.8	Normal	Normal

and the level of the sulfonamide in the gall bladder bile and in the venous blood was determined. Doubilet's method of analysis, as described by Carryer and Ivy,<sup>3</sup> was used for the bile, and the procedure of Marshall and Litchfield<sup>7</sup> was used for the blood. The gall bladder wall was examined grossly and microscopically to dismiss the possibility of disturbance of the blood supply.

#### RESULTS

In each case, examination of the dog at the time of completion of the experiment showed that the ligature obstructed the cystic duct without interfering with the blood supply of the gall bladder. Gross and microscopic examination of the gall bladder wall confirmed the fact that its blood supply had not been disturbed. Sulfonamide was not found in any of the specimens of gall bladder bile (see Table II), in spite of high blood levels. In these experiments, obstruction of the cystic duct prevented sulfanilamide, sulfathiazole, and sulfadiazine from entering the gall bladder.

#### SUMMARY

It is well known that the sulfonamides are excreted in the bile in man and in animals. Furthermore, Bettman and Spier<sup>2</sup> have demonstrated that these drugs are concentrated in a gall bladder which functions normally. Our experiments show that sulfanilamide, sulfathiazole, and sulfadiazine do not enter the gall bladder of the dog when the cystic duct is occluded. They do not pass through the wall of the vesicle to reach the gall bladder bile.

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TABLE II

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CASE 2—A. D., a 14 year old colored male, was admitted to the surgical service with a chief complaint of abdominal pain. Three days prior to admission the boy began to experience crampy pain in the umbilical region. This was associated with nausea but not vomiting. On the day of onset of the abdominal pain the patient had several loose bowel movements.

Physical examination was essentially negative except for the abdominal findings. The abdomen was symmetrical; there was tenderness in the right lower quadrant. There was no rigidity.

There were 10,300 white blood cells, 72 per cent polymorphonuclear, 12 per cent lymphocytes, 6 per cent monocytes, and 10 per cent eosinophiles. Despite the absence of rigidity the patient was placed on surgical liquids and prepared for exploratory laparotomy. In the interim typical urticarial wheals appeared. These wheals and the abdominal symptoms responded promptly to the administration of ephedrine.

Questioning then revealed that the patient had received antitoxin for a laceration of his hand the previous day. It may be assumed, therefore, that the patient suffered from an accelerated serum reaction.

#### DISCUSSION

To gain an understanding of present concepts of serum sickness, it is necessary to look back to the work of Richet<sup>2</sup> and his collaborators that was done at the turn of the present century. Richet, while sojourning on the yacht of the Prince of Monaco in the Indian Ocean, undertook the study of the urticating principle of the Portuguese man of war, a variety of sea nettle or stinging jelly fish. He considered the urticating principle a toxin and injected into dogs extracts made from these nettles. To his surprise he found that although the first injection was harmless, the second injection made some days later provoked severe, and at times, fatal reactions. He considered that the first injection removed the animal's natural immunity to this toxin, hence a state of anaphylaxis existed. This was not the correct explanation; it would have remained an academic question, however, had not the introduction of diphtheria antitoxic sera by von Behring<sup>3</sup> produced in humans a state strikingly parallel to the anaphylactic animal.

A completely satisfactory explanation of serum sickness eludes us even today. Certain facts, however, are known, thus, during and following serum disease induced by the injection of immune animal serum, circulating antibodies may be found in the blood. These antibodies are not constant but vary quantitatively and qualitatively in different cases. They include precipitans (anaphylactic antibodies), heterophile antibodies, and atopic reagents. Precipitins are frequently found in the blood of human beings following the administration of immune animal serum, but such precipitins may occur without the development of serum disease. Furthermore, they are regularly absent in the blood of patients treated with normal horse serum even in the presence of typical serum sickness (Harten and Walzer<sup>4</sup>). Atopic reagents (Prausnitz-Kustner or skin-sensitizing antibodies) occur frequently but by no means regularly following the administration of therapeutic serum. Heterophile antibodies

## SERUM SICKNESS SIMULATING ACUTE ABDOMINAL DISORDERS

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SEVERE abdominal pain, as Duke<sup>1</sup> has aptly pointed out, is a symptom which is never taken lightly by a careful physician. It often indicates a severe illness; in fact, it often indicates an emergency. However, abdominal pain which may simulate in some respects the pain caused by severe abdominal disease is occasionally the result of hypersensitiveness to a foreign serum. Abdominal pain sometimes occurs without other manifestations of serum sickness, or rather, it may be the sole striking symptom of serum allergy. In such a case, the real cause of the pain may not be apparent and an error in diagnosis can easily be made. Although cases have been reported in which an allergic state has simulated the acute abdomen, these have been due to ingestants, and we have been able to find none in which the responsible agent was parenterally administered prophylactic or therapeutic sera. In view of the increasing use of such sera in civil as well as military life it is felt that the recognition of the abdominal features of serum sickness will become of progressively greater importance.

Our illustrative cases have been selected from a larger number and represent typical histories of patients who have abdominal pain as the outstanding symptom of serum hypersensitivity.

### CASE REPORTS

CASE 1.—C. H., a 17 year old colored male, was admitted to the observation ward stating that he had been seized with a severe abdominal pain two hours previously. There was no nausea, vomiting, or loose stools. There had been no previous history of indigestion. Physical examination revealed generalized rigidity of the abdomen. The temperature was 100° F. There were 9,500 white blood cells, 91 per cent neutrophils, and 9 per cent small monocytes. The urine was negative. The possibility of a perforated viscus was entertained and the patient was x-rayed to rule this out. The pain was so excruciating that although  $\frac{1}{6}$  gr. morphia had been administered to relieve apprehension, severe discomfort necessitated the administration of a second dose of the drug. The patient was prepared for operation. An ice cap was applied to the abdomen and the patient was kept in the observation room overnight. At seven o'clock in the morning it was noticed that the patient had a generalized urticaria associated with marked itching. It was then learned that he had received antitetanic serum for a dog bite three days previously. The urticaria and pruritus responded to the administration of epinephrine and the application of calamine lotion.

strongly to the addition of the antigen. The gall bladder contracted during shock but the sphincter contracted to a greater extent, thus no emptying occurred. Hence we have a type of biliary colic on a dyskinetic mechanism. Couvelaire and Bargeton<sup>15</sup> sensitized dogs to horse serum by intravenous administration; on re-exposure to the antigen by injection of serum into the duodenopancreatic vein and directly into the pancreas itself, although no general shock resulted, an immediate local persistent edema of the pancreas became apparent. When the animal was sacrificed the next day the peritoneal cavity was found to contain serosanguineous fluid and on the omentum were several whitish areas having the appearance of fatty necrosis. The pancreas was edematous and contained multiple hemorrhages. One cannot but be struck by the similarity of these lesions to those found in acute hemorrhagic pancreatitis. It is well known that in about one-half the cases a stone in the ampulla of Vater leads to a diversion of bile into the pancreatic ducts. According to Bloomfield<sup>16</sup> no anatomic reason for entry of abnormal material into the pancreatic ducts can be demonstrated in many instances. We suggest that these cases of acute hemorrhagic pancreatitis may represent a fulminating type of allergic reaction.

Granted that these lesions may be demonstrated in the experimental animal, the question may fairly be asked whether similar conditions have been observed in the human being. Speaking of the gastrointestinal tract in angioneurotic edema, Osler<sup>17</sup> stated that ten of his patients had colic; he considered that the nature of the local trouble was known, as exploratory operations confirmed his view that it was an edema of the wall of the bowel. In a case reported by Morris,<sup>18</sup> in washing out the stomach to relieve the severe vomiting, a portion of the mucosa was removed and on examination was found to be in a state of acute edema. Osler described the colic of intestinal angioneurotic edema with great clarity. In his experience it came on suddenly and often reached an extreme grade. As a rule it occurred with the skin manifestations, but at times it was the only feature, and often there was no clue as to the nature of the trouble. In the majority of cases the pain was central, more or less continuous with paroxysms of greater intensity. The patient tended to roll about in bed or be doubled up in an agony of pain. The abdominal walls were tense; appendicitis, gallstone, or renal colic were suspected and in a considerable number of his cases laparotomy was performed. In severe attacks vomiting occurred with the pain and lasted many hours. The patient looked very ill, with pallor, small pulse, and features of collapse; at the end of ten or twelve hours the symptoms often disappeared, an outbreak of local edema giving a hint concerning the diagnosis. He noted that with gastric symptoms and colic there sometimes occurred diarrhea, meteorism, and even the passage of blood.

A case reported by Bogart<sup>19</sup> is of especial interest. The patient presented the picture of a very severe illness requiring operative relief.

(hemolysins and agglutinins for sheep red blood cells) occur in the blood after serum has been given. An analysis of all the available data still fails to reveal a constant association of any type of antibodies with serum sickness. One is compelled to conclude with Harten and Walzer that the mechanism of serum sickness cannot be correlated with any of the antibodies which have thus far been detected in this condition. Indeed Coca's<sup>5</sup> theory that the symptoms of serum disease are due to specific altered reactivity of the protoplasm of some of the body cells which is not mediated by antibodies has not yet been controverted.

Perhaps the major phenomena of serum sickness are due, as Foshay and Hagebusch<sup>6</sup> suggest, to a release of histamine or a histamine-like substance into the circulation consequent on the union of serum protein antigen and antibodies. Certainly the brilliant experimental work of Katz<sup>7</sup> demonstrates clearly that histamine is intimately concerned with the production of the allergic state; many gaps in our knowledge of the exact role of histamine (or similar substances) remain to be filled in. Regardless of the precise nature of the underlying mechanism, the pathology of the allergic or anaphylactic state seems to be fairly well agreed upon. Contraction of smooth muscle, capillary dilatation with edema, and diapedesis of red cells (which may progress to hemorrhage) and eosinophilic infiltration in one or another combination produce the signs and symptoms which are recognized clinically and experimentally.

It is not clear why certain tissues or organs should be affected in serum disease to the exclusion of others; it is known, however, that they may be locally sensitized or more highly reactive than others. That this local sensitivity was on a cellular rather than a humoral basis has been demonstrated by experimental work. Friedmann<sup>8</sup> and Otto<sup>9</sup> as well as Doerr<sup>10</sup> showed that in the process of passive sensitization, in which the blood of a sensitized guinea pig is transferred into a normal nonsensitive guinea pig, the latter does not become sensitized until after an interval of at least four hours. Indeed, twenty-four to forty-eight hours must elapse before maximum passive sensitization has been accomplished. This interval is required presumably for the antibodies to be firmly attached to the tissue cells (Vaughan<sup>11</sup>). Schultz<sup>12</sup> found that if, after the first injection of foreign serum, a long enough interval elapsed, intestinal muscle would show a supranormal degree of irritability toward the same serum. After washing strips of sensitized intestinal smooth muscle free from blood he found that contact with the specific antigen caused an anaphylactic response with muscular contraction. Dale<sup>13</sup> improved on the Schultz technique, developing the uterine strip method which has since become a routine procedure in the study of sensitization.

That other abdominal viscera may partake of the general sensitization has been demonstrated in the instance of the gall bladder by Deissler and Higgins.<sup>14</sup> Strips and isolated whole gall bladders from guinea pigs previously sensitized to horse serum and egg white were found to react

strongly to the addition of the antigen. The gall bladder contracted during shock but the sphincter contracted to a greater extent, thus no emptying occurred. Hence we have a type of biliary colic on a dyskinetic mechanism. Couvelaire and Bargeton<sup>15</sup> sensitized dogs to horse serum by intravenous administration; on re-exposure to the antigen by injection of serum into the duodenopancreatic vein and directly into the pancreas itself, although no general shock resulted, an immediate local persistent edema of the pancreas became apparent. When the animal was sacrificed the next day the peritoneal cavity was found to contain serosanguineous fluid and on the omentum were several whitish areas having the appearance of fatty necrosis. The pancreas was edematous and contained multiple hemorrhages. One cannot but be struck by the similarity of these lesions to those found in acute hemorrhagic pancreatitis. It is well known that in about one-half the cases a stone in the ampulla of Vater leads to a diversion of bile into the pancreatic ducts. According to Bloomfield<sup>16</sup> no anatomic reason for entry of abnormal material into the pancreatic ducts can be demonstrated in many instances. We suggest that these cases of acute hemorrhagic pancreatitis may represent a fulminating type of allergic reaction.

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A case reported by Bogart<sup>19</sup> is of especial interest. The patient presented the picture of a very severe illness requiring operative relief.

The abdomen having been opened, the jejunum was found to be quite swollen and edematous. This swelling and edema extended up to the point where the intestine passed beneath the mesentery and was so pronounced as to produce a stiffening of the intestine sufficient to prevent peristalsis; when grasped between the forefinger and thumb the intestine was apparently at least one inch in thickness. Evidently the lumen was almost if not entirely occluded. The patient gradually convalesced after the operation, recovering after seventeen days.

Alexander and Eyermann<sup>20</sup> have expressed the opinion that there seems to be a close relation between Henoch's purpura and acute intestinal allergy due to the ingestion of foods; in both, spasm of portions of the intestinal musculature is demonstrable with the x-ray, and peritoneal urticaria and hemorrhage with edema of the bowel wall are demonstrable on laparotomy. In describing the symptoms of Henoch's purpura, Piness and Miller<sup>21</sup> state that not infrequently it closely simulates the acute abdomen.

The treatment of the acute abdominal crisis due to serum sickness is the treatment of the latter condition generally, namely the exhibition of the sympathomimetic drugs. It is necessary, of course, that a diagnosis be made; where skin or joint manifestations are concomitant, the situation is obvious at a glance, where this is not the case the presence of recent wounds treated prophylactically with antitetanic serum, or a history of recent illness treated with therapeutic sera should give one the clue to the true state of affairs.

#### SUMMARY

Case reports of serum disease simulating the acute abdomen are presented. Possible etiologic mechanisms drawn from a brief survey of experimental and clinical publications are given.

In view of increasing prophylactic and therapeutic use of sera it is felt that recognition of the abdominal features of serum sickness will be of progressively increasing importance.

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# Editorial

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## Dicoumarin and Prophylactic Anticoagulants in Intravascular Thrombosis

THAT cattle are sometimes affected by a hemorrhagic disease which seems to develop for no apparent reason and is occasionally fatal has long been common knowledge among veterinarians and cattle raisers. However, it was not until relatively recently that the explanation for this phenomenon was given by two veterinarian investigators, Schofield, in Canada, and Roderick, at the North Dakota Agricultural Experimental Station. Their studies showed conclusively that the disease was due to the eating of improperly cured hay or spoiled sweet clover silage and the condition became known as sweetclover disease of cattle. In 1934, Professor Karl Paul Link and his associates, of the Wisconsin Agricultural Experimental Station at the University of Wisconsin, became interested in this phenomenon and began experimenting to determine the causal factor of hemorrhage in the spoiled fodder. Seven years later, these carefully conducted and brilliantly conceived series of investigations were culminated with the isolation and synthesis of the hemorrhagic agent in spoiled sweet clover, dicoumarin, 3,3'-methylene-bis-(4-hydroxycoumarin), a white crystalline substance readily soluble in alkaline solutions but only slightly soluble in water.

Intensive studies have since been undertaken to determine the pharmacologic and therapeutic action of dicoumarin. Accordingly, it has been found that the principal effects of dicoumarin are prolongation in prothrombin time and delay in coagulation of blood. Following its administration, either orally or intravenously, a variable lag period of from twenty-four to seventy-two hours exists before this action becomes manifest. Although there is some evidence to support the belief that dicoumarin produces physiologic inhibition of prothrombin formation in the liver, or destruction or suppression of prothrombin activity, its exact mechanism of action has not been definitely established. Apparently, orally or intravenously administered vitamin K produces little or no effect on the hypoprothrombinemia or on the hemorrhagic manifestations which follow the use of dicoumarin. Indeed, it would seem that this can be influenced only by means of transfusions of fresh whole blood or plasma. Other studies have shown that dicoumarin has a tendency to impair clot retraction and increase the sedimentation rate of erythrocytes, but it seems to produce no significant changes in erythro-

cyte or leucocyte counts, in the fragility of erythrocytes and blood platelets, in the hepatic and kidney functions, and in the values for non-protein nitrogen, blood sugar, bilirubin, and calcium in the blood. Prolonged excessive doses of dicoumarin almost invariably result in fatal hemorrhage, but no significant pathologic changes except those due to bleeding into the tissues have been found on necropsy studies.

The anticoagulant property of dicoumarin forms the basis of its therapeutic significance. Accordingly, its obvious theoretic value clinically would be in the prophylaxis of intravascular thrombosis. Heparin, which has the disadvantages of being costly, requiring continuous or repeated intravenous injections, and of maintaining a constant anticoagulant effect with difficulty, has been the most recently developed and widely heralded agent for this purpose. If dicoumarin could be shown to be as good as, or superior to, heparin in this respect, it would have a decidedly practical advantage. Workers interested in blood and peripheral vascular diseases, therefore, eagerly seized upon this new anticoagulant agent and began studies to evaluate its clinical efficacy in the prophylaxis and treatment of postoperative thrombosis and phlebitis, pulmonary embolism and infarction, coronary thrombosis, and peripheral vascular disease. The results of these preliminary studies have appeared in recent issues of current journals. Allen and his co-workers, at the Mayo Clinic, administered dicoumarin in 374 cases "in an effort to prevent arterial or venous thrombosis and pulmonary embolism or to prevent extension of intravascular thrombosis." Three of these patients developed clinical thrombosis in spite of the fact that the prothrombin time was elevated. Accordingly, the authors concluded that these observations and their experimental studies "strongly suggest the value of administering dicoumarin in preventing intravascular thrombosis." Somewhat similar studies and conclusions were also reported by other observers.

Several considerations may be introduced to support the cautious position of provisional reluctance in accepting these conclusions. Notwithstanding certain implications, the statistical significance of the reported results upon which many of the conclusions are based is open to question because the series of investigations is not adequate nor are the results sufficiently impressive to justify definite statements. This is clearly demonstrated by a comparison with other incidences of postoperative thrombosis in cases not receiving anticoagulant prophylactic measures. Thus, in a series of 4,410 consecutive operations performed at the Charity Hospital, in New Orleans, exclusive of procedures on the eye, ear, nose, and throat, there were only 3 (or 0.06 per cent) cases of postoperative thrombophlebitis. Even more significant is the fact that better results have been reported following the use of much simpler, safer, and more economical prophylactic measures than the administration of dicoumarin or other anticoagulant agents. Thus, Zava, using early ambulation

postoperatively, reported over 6,000 surgical cases, many of which were gynecologic, without a single occurrence of embolism. In addition to these considerations is the fact that dicoumarin, like other anticoagulants, possesses certain hazardous features. Of these, the most important is hemorrhage, which in surgical cases obviously assumes even greater significance. Hemorrhage occurred in 31 cases in the series reported by the Mayo investigators, 24 of which occurred from the operative site; 1 was fatal. There were 2 other fatal cases apparently as a result of hemorrhage in patients with subacute bacterial endocarditis. The authors believe that dicoumarin is contraindicated in such cases, because in these patients there is apparently an increased tendency to bleed. Attention is also directed to certain other conditions in which the drug should be employed cautiously or not at all. These include renal insufficiency or those with an already prolonged prothrombin time, such as obstructive jaundice or other vitamin K deficient diseases. The fact that there exist wide and as yet unexplained variations in the prothrombin and hemorrhagic response to dicoumarin in different individuals, emphasizes further the practical significance of these jeopardous features.

It becomes apparent from these considerations, therefore, that, for the present, dicoumarin cannot be regarded as a safe, efficacious, and satisfactory prophylactic or therapeutic agent in intravascular thrombosis. In recent years, there has been a revival of interest in the use of anticoagulants for this purpose. Until the arrival of dicoumarin, heparin had received the most assiduous attention and intensive efforts of investigators in this field. The fact that workers are already seeking a substitute demonstrates clearly that heparin did not prove completely satisfactory. In the prophylaxis and treatment of intravascular thrombosis, certain difficulties and objectionable features must be overcome before any anticoagulant can be considered entirely satisfactory and its use become widely adopted. The prophylactic value of any anticoagulant agent is manifestly difficult to establish in such notorious unpredictable conditions as intravascular thrombosis. Further emphasis is placed upon the undesirability of this particular characteristic by the fact that the anticoagulant agent must be employed in all cases, which is obviously impractical. This is especially true in view of the danger of hemorrhage which may follow the use of an anticoagulant agent and which assumes obvious significance in surgical cases. Therapeutically the use of an anticoagulant in intravascular thrombosis has at least the theoretical objection of increasing the tendency of embolism. That this is not entirely theoretic, however, is shown by our experience with a patient, who, while heparinized over a period of four weeks, had five nonfatal emboli. Obviously in such cases the more certain means of preventing propagation of the thrombus or embolization is by proximal vein ligation. In view of the present lack of trenchant knowledge con-

cerning the etiologic factors in intravascular thrombosis the rationale of anticoagulants as combative measures may be justifiably questioned. These protesting considerations to the prophylactic and therapeutic use of all anticoagulants in intravascular thromboses are not intended as critical disapprobation but rather as criticism in its strict etymologic sense, that is, evaluation. A restatement of facts is frequently necessary to dispel the fog of enthusiasm and thus permit a clear discernment of objectives.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## AMEBIC HEPATITIS AND HEPATIC ABSCESS

AN ANALYSIS OF 181 CASES WITH REVIEW OF THE LITERATURE

ALTON OCHSNER, M.D., AND MICHAEL DEBAKEY, M.D.

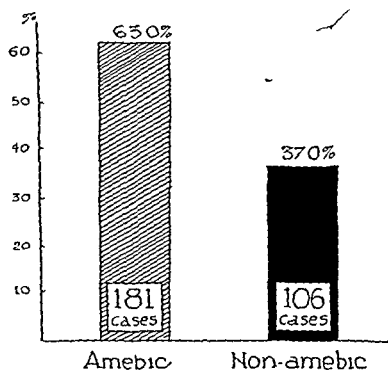
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IN PREVIOUS publications we<sup>277, 287</sup> presented an analysis of 73 patients with amebic hepatitis and hepatic abscess, admitted to the Charity Hospital and the Touro Infirmary during the six-year period, 1928 to 1933 inclusive, and 66 patients admitted to these institutions during the four-year period, 1934 to 1937 inclusive. Since then, i.e., during the four-year period 1938 to 1941 inclusive, there have been 42 cases of amebic hepatitis and hepatic abscess.<sup>288</sup> During this fourteen-year period there have been 287 patients with liver abscess admitted to the Charity Hospital and Touro Infirmary in New Orleans and of this number 181 (63 per cent) were amebic and 106 (37 per cent) were nonamebic (Graph I). Whereas the present report is based upon a study of the total number, 181 patients admitted during the fourteen-year period, 1928 to 1941 inclusive, significant comparisons of the three groups will be considered wherever desirable. In addition to this an attempt has been made to review the literature and present a comprehensive survey of the subject. While the literature was reviewed up to 1937 in a previous publication, in the present report this is brought up to date and for purpose of convenience and because of the relative inaccessibility of the previous publication much of this material is included.

*History.*—A historical consideration of amebic hepatic abscess must necessarily include that of amebic dysentery. Whereas knowledge concerning suppurative disease of the liver has existed since the time of Hippocrates and perhaps earlier, the realization of amebic hepatic abscess as a separate clinical entity is of relatively recent origin. In a comprehensive exposition of the subject, Bertrand and Fontan<sup>21</sup> presented an excellent historiographic résumé of the former. The causal relationship between amebic dysentery and amebic abscess was considered as early as 1818, by Ballengal<sup>10</sup> and later by Annesley,<sup>6</sup> Budd,<sup>37</sup> Dutroulau,<sup>106</sup> and others even before the ameba was described, but its true character was not established until after the causal agent of amebic dysentery was recognized.

During this early period it appears that the relationship between dysentery and hepatic abscess was recognized especially by the observers in India, whereas most European investigators did not consider it significant. In his consideration of liver abscess occurring in India, Annesley, in 1828, directed attention to the frequent association of these two conditions and accurately described the ulcerative lesion in the large bowel. Although he realized the difficulty of establishing an etiologic relationship, he expressed his conviction that "abscess of the liver is in some cases consequent on dysentery, and caused by it," a conclusion reached by Budd in his investigations of the subject twenty-five years later. This subject, however, remained controversial for many years later and even after the isolation of the ameba. Frerichs,<sup>129</sup> the eminent German pathologist and internist, severely criticized the views held by Annesley and Budd and stated, in 1879, that, "It has been far too generally assumed that the dysentery precedes the hepatic inflammation; almost all physicians who have acquired their experience in warm



Graph I.—Relative incidence of amebic and nonamebic hepatic abscesses in 287 patients admitted to Charity Hospital and Touro Infirmary during the 14-year period, 1928 to 1941, inclusive.

climates have arrived at the conviction that the dysentery is often preceded by the hepatitis, or that the two may be developed simultaneously, and that hepatitis frequently occurs without any disease of the intestine." He states further that "a careful analysis of cases of this nature is entirely opposed to the idea of their connection with intestinal ulceration. Moreover, as regards the cases where the dysenteric ulceration of the intestine has preceded the development of the abscesses of the liver, it has not yet been proved that the hepatic disease is the result of the intestinal infection, and, above all, no one has succeeded in demonstrating, as the connecting link, any implication of the roots of the portal vein in the intestinal inflammation, or an intestinal pyelephlebitis." These disputations were continued as late as 1898 and Rogers,<sup>325</sup> in his Lettsonian Lectures, directs attention to the "completely contradictory statements in the articles on dysentery and liver abscess in the first edition of Allbutt's System of Medicine by Davidson and

Lasfleur respectively." The former author<sup>23</sup> considered liver abscess occurring in tropical or subtropical countries as "an uncomplicated disease, and that when complicated with dysentery it not infrequently precedes it" and contended that it was due to a primary hepatic insufficiency consequent to residence in a hot climate which "favors the settlement and growth of pyogenetic organisms in the liver, quite apart from any dysenteric complications . . ." In contradistinction to this hypothesis, Lasfleur<sup>201</sup> described clearly the pathogenesis of amebic dysentery and its complication, hepatic abscess, and attributed the process to the direct activities of the ameba. Even up to the turn of the present century the subject remained controversial and as expressed by Rogers,<sup>325</sup> "in spite of the valuable work, especially by Kartulis and Councilman and Lasfleur, medical opinion in 1902, particularly in India, was against the recognition of amebic dysentery as a distinct disease and also to a great extent contrary to its acceptance as the causative agent of tropical liver abscess, while there were still great differences of opinion as to whether such abscesses were in any way directly associated with dysentery."

Credit for the discovery of the *Endameba histolytica* is usually given to Lösch,<sup>214</sup> (1875). However, it should be realized that although he successfully reproduced the disease in one of four dogs by contaminating their food and injecting them rectally with stools containing the motile amebae, he did not consider the ameba as the cause of the disease but merely suggested that their presence delayed healing of the ulcerations. Koch,<sup>197</sup> in 1883, stated that he had observed amebae in material obtained from colonic ulcers of five patients dying of dysentery in Egypt. Two of these cases were complicated with liver abscess, and because in one amebae were found in the capillaries and tissues adjoining the abscess, he considered their possible etiologic significance. Perhaps Kartulis<sup>191</sup> presented one of the most important early contributions toward the recognition of the etiology of amebic dysentery and its complication, liver abscess. In 1886, he published the results of his investigation of 150 cases of dysentery in Egypt. He demonstrated amebae, similar to those previously described by Lösch, in ulcers and in tissue beneath ulcers of sections of diseased intestines, and concluded that these protozoa were the cause of "tropical dysentery." He stated subsequently<sup>192, 193</sup> that he had found similar amebae in the pus of liver abscesses and that it was the causal agent of hepatic abscess associated with dysentery in the tropics. As stated previously, in viewing retrospectively the then current controversy which apparently raged concerning the etiology of "tropical dysentery" and associated liver abscess, it is of curious interest, in the light of subsequent development, to read the severely critical attack of Kartulis' conclusions launched by Bertrand and Fontan<sup>21</sup> in their extensive treatise published in 1895, and the argumentative defense of their view that liver abscess associated

with dysentery is caused primarily by invasion of pyogenic micro-organisms and that amebae might play a secondary but not a specific role.

Numerous investigators subsequently confirmed Kartulis' observations. One year after Kartulis' publication, Jarosloy Hlava<sup>165</sup> demonstrated amebae in sixty cases of dysentery occurring in Prague and successfully reproduced the disease in four of six cats by intrarectal inoculation of dysenteric stools obtained from human beings. In this connection there is an interesting and rather curious story which has medico-literary significance. For over fifty years these observations of Hlava were credited in textbooks and periodicals on the subject, to "Dr. O. Uplavici."<sup>379</sup> Several years ago Dobell<sup>101</sup> unmasked this mysterious character. It appears that Hlava<sup>165</sup> published his original article in a relatively inaccessible Czechoslovakian journal with the title, "O Ůplavici. Predbezné sdelení" (On Dysentery. Preliminary Communication). According to Dobell no translation or further communication was ever published and subsequent investigators have referred to the brief review or abstract of this article signed by Kartulis and appearing in the *Centralblatt für Bakteriologie und Parasitenkunde*.<sup>379</sup> Extraordinary as it may seem, Hlava's name was completely omitted in this abstract and only the title of his paper was presented as "Uplavici, O."<sup>379</sup> Moreover, not only did Kartulis refer to the author personally as Uplavici but in the contents of the issue in which the abstract appears the name is given as "Uplavici, O." By 1910, "Uplavici, O." was listed in the *Index Catalogue of Medical and Veterinary Zoology*, as having acquired a doctor's degree. As stated by Dobell, the mysterious "Dr. O. Uplavici" has haunted respectable books and periodicals long enough and it "seems high time that this ghost should be laid once and for all."

Of no less historical importance are the investigations in this country. Osler,<sup>291</sup> in 1890, observed amebae in a liver abscess of a patient operated upon and in whom amebae were found subsequently in the stools. Shortly afterward, similar observations were made by Stengel,<sup>356</sup> Musser and Willard,<sup>203</sup> and Dock.<sup>103</sup> In 1891, Councilman and Lafleur<sup>70</sup> presented their classical contribution based upon a perspicuous investigation of fifteen cases of amebic dysentery and six complicating liver abscesses. These studies conclusively established "amebic dysentery" and its complication "amebic abscess of the liver" as clinical entities with the ameba as the specific etiologic agent. Indubitable corroborative evidence of this fact was supplied by Kovács,<sup>290</sup> in 1892, who successfully produced dysentery in kittens with amebae from dysentery cases in human beings, and by Kruse and Pasquale,<sup>201</sup> in 1894, who successfully produced characteristic dysentery in a cat by intrarectal instillation of sterile liver abscess pus containing amebae. In 1901, Harris<sup>155</sup> also accomplished, perhaps for the first time in puppies, successful experimental production of amebic hepatic abscess following experi-



mentally produced amebic dysentery. Subsequently, similar results were obtained in cats by Craig,<sup>76</sup> Huber,<sup>181</sup> and others.<sup>9, 91, 391</sup>

The important extensive clinical investigations of amebic hepatic abscess by Sir Leonard Rogers deserve mention in any historical consideration of the subject. Approximately four decades ago<sup>320</sup> this investigator demonstrated that whereas active amebae were frequently not present in the "pus" they were constantly found in the wall of tropical abscesses of the liver and that in the majority of instances pyogenic organisms were absent from these abscesses when they were first opened. He immediately realized the significance of this fact and directed attention to the importance of treating the abscesses conservatively with aspiration and emetine, which will be considered in greater detail under the discussion of therapy. Of interest in this connection is a recent article of Huard, Long, and Graziana<sup>171</sup> in which a Dr. Florence<sup>125</sup> is cited as antedating Rogers in the use of emetine therapy. They state that Dr. Florence employed hypodermic injections of emetine as early as 1882.

*Incidence.*—Intensive studies during the past decade have clearly established the relative frequency and increasing significance of amebiasis. In spite of the well-established fact that amebiasis is of ubiquitous occurrence, the fallacious impression still exists that amebiasis is an acute disease usually contracted in the tropics and manifested principally by dysentery or liver abscess. Its universal distribution has been conclusively demonstrated by extensive surveys made in various parts of the world. As aptly expressed by Faust,<sup>118</sup> "*Endamoeba histolytica* has been found wherever careful coprological surveys have been made on the human population, from Saskatchewan, Canada (52° 30' N.) to the Strait of Magellan (52° S.)." Its prevalence in the United States has been emphasized repeatedly by Craig<sup>72</sup> who is of the opinion that between 5 and 10 per cent of this country's population harbor the parasite. That this is not an exaggerated estimate is clearly demonstrated by the results of numerous surveys in various parts of the country. Indeed, on the basis of more recent investigations Faust<sup>118</sup> concludes that "the incidence figure may possibly average as high as 20 per cent, or double that of previous accepted estimates." As early as 1911, Sistrunk<sup>347</sup> directed attention to its frequency here and found it present in 17.2 per cent of 145 patients examined at the Mayo Clinic. Subsequent studies in this institution revealed an incidence of 22.5 and 7.9 per cent, respectively.<sup>228, 338</sup> In the Veterans Bureau Hospital in California, Wight<sup>393</sup> observed an incidence of 6.8 per cent and Meleney, Bishop, and Leathers<sup>244</sup> found it to be 11.4 per cent in an examination of 20,237 individuals in Tennessee. Faust<sup>114</sup> reported a 20 per cent incidence in one county in Virginia and 13.7 per cent in an examination of 1,100 individuals in New Orleans. Craig<sup>83</sup> found a 12.7 per cent incidence in an examination of 189 officers of the Medical Corps of the United States Army. In 1934, Craig<sup>85</sup> reported the results of a collection of the most important surveys made in various

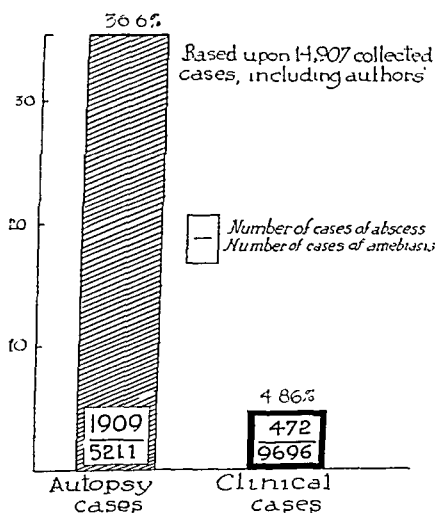
parts of the country and found an incidence of 11.6 per cent in 49,336 individuals examined. Moreover, it would seem that the incidence of infection is increasing. Thus, in a collected series of 19,882 individuals examined before 1930 there was a positive incidence of 10.3 per cent,<sup>109</sup> whereas in a similarly collected group of 28,634 individuals examined since 1930 the incidence was 12.8 per cent.<sup>110</sup> However, as recently emphasized by Faust<sup>118</sup> such surveys are "too few and too fragmentary to provide a complete demographic picture of the infection. For many areas no surveys have been undertaken; for many others the data are based on unrepresentative groups of the population or too few persons have been examined to provide significant statistics. Moreover, most surveys have employed a single technique on a single stool specimen; hence the positive cases reported constitute only a fraction of the true incidence in the particular area." Accordingly, it is his authoritative opinion that, "In the population of the United States an average amebiasis incidence as high as 20 per cent may be reached, rather than the accepted figure of 5 to 10 per cent."

Thus, it would seem that Craig's estimate that between six million and twelve million people in this country are infected with this parasite is too conservative and that a figure of twenty to twenty-five million would be more accurate. The surgical significance of this appallingly high incidence lies in the potential development of hepatic infections. In a previous publication<sup>287</sup> it was shown that approximately 4 to 5 per cent of individuals with intestinal amebiasis develop hepatic complications. Accordingly, on the basis that twenty million people in this country are infected with *E. histolytica*, the potential number of hepatic complications is approximately one million. Such an astounding figure emphasizes with striking clarity the full significance of this important complication.

It is obviously difficult to determine accurately the relative occurrence of complicating amebic hepatitis and hepatic abscess in intestinal amebiasis. The reported statistics vary considerably and depend upon a number of factors. Thus, statistical analyses based upon post-mortem cases will reveal a much higher incidence of hepatic abscess than those based upon clinically observed infections. Obviously, the former cases include patients with more severe amebic infections who are more likely to have complicating liver abscess which is often the cause of death. Moreover, autopsy studies permit more accurate determination of extra-intestinal amebic involvement. In a collected series of 5211 fatal cases of amebiasis,<sup>111</sup> 36.6 per cent were found to have hepatic abscess (Graph II). The lowest incidence in this group was 7.6 per cent<sup>8</sup> and the highest was 84.4 per cent.<sup>149</sup>

As previously stated, the incidence of hepatic abscess in all cases of intestinal amebiasis varies according to different reports and seems to depend upon whether the cases were ambulatory or not. Thus, Fletcher<sup>132</sup> reported 27 cases (22.6 per cent) of hepatic abscess in 119 cases of intestinal amebiasis at the Johns Hopkins Hospital. Buchanan,<sup>73</sup>

on the other hand, found that in India the ratio of hepatic abscess to intestinal amebiasis was 1 to 628 in the natives and 1 to 18 in the Europeans. In Peiping, Tao<sup>265</sup> observed an incidence of 1.8 per cent in 1,000 cases of positive amebic infections. In a collected series of 9,696 cases of clinical amebiasis, including the authors', there were 472 cases of amebic abscess of the liver, an incidence of 4.86 per cent<sup>412</sup> (Graph II). In the Charity Hospital group of our series there were 160 cases of amebic hepatic abscess among 1333 cases of amebic dysentery, an incidence of 17.4 per cent. There has been a curious change in the incidence during the fourteen-year period in this institution. Thus, during the six-year period, 1928 to 1933 inclusive, there were 59 (or 15.2 per cent) cases of amebic hepatic abscess among 388 cases of intestinal amebiasis.<sup>277</sup> During the four-year period, 1934 to 1937 inclusive, these respective figures were 59 (or 20.4 per cent) and 288.<sup>287</sup> More recently during the four-year period, 1938 to 1941 inclusive, there



Graph II.—Relative incidence of amebic hepatic abscess in fatal and clinical amebiasis.

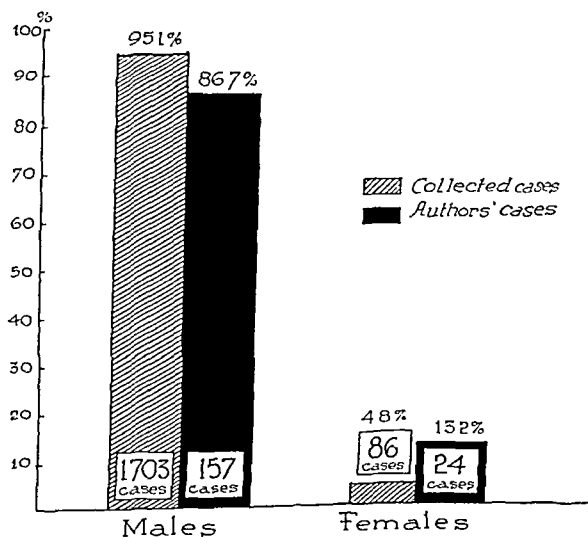
were only 42 (or 6.4 per cent) cases of amebic hepatic abscess in 657 cases of intestinal amebiasis.<sup>285</sup> Thus, it would seem that the incidence of amebiasis has continued to increase but the incidence of complicating hepatic abscess has been decreasing during the last four years although it was increasing up to that time. This would suggest that intestinal amebiasis is being recognized earlier and treated more effectively in recent years. However, as emphasized by Craig,<sup>65</sup> many cases remain undiagnosed especially in the temperate climates where amebiasis is still considered a tropical disease by too many physicians. This author<sup>65</sup> has on numerous occasions found an amebic hepatic abscess at autopsy that was entirely unsuspected before death.

The incidence of amebic hepatitis and hepatic abscess in hospital admissions also varies considerably in different localities and in many in-

stances does not conform to the incidence of amebiasis in the same locality. At the Charity Hospital in New Orleans, during the fourteen-year period, 1928 to 1941 inclusive, there were 784,622 total admissions, among which there were 160 patients with amebic abscesses and 101 with pyogenic abscesses with respective incidences of 0.020 and 0.0128 per cent of the total admissions. During the same period there were 2,538 patients diagnosed as having liver disease, of which 160 (or 6.3 per cent) had amebic hepatic abscess and 101 (or 3.9 per cent) had pyogenic abscesses. In 3,115 hospital surgical patients, Eolian<sup>112</sup> found amebic liver abscess to be present in 0.28 per cent. In Ceylon, Wijerama<sup>394</sup> found an incidence of 1.2 per cent among 4,070 hospital admissions. In South Carolina, Young and Bristow<sup>404</sup> report an incidence of 0.07 per cent in 34,994 total hospital admissions. As commented upon previously,<sup>287</sup> the unusually low incidence of 0.000017 per cent reported by Goldburgh,<sup>141</sup> based upon 120,000 admissions at the Jefferson Hospital and 232,000 admissions at the Philadelphia General Hospital, is rather difficult to explain. Whereas the relative incidence of amebic abscess is considerably greater in the Charity Hospital series (0.034 per cent) than in the Philadelphia group (0.000017 per cent) it is our opinion that this marked difference cannot be explained solely by the slightly higher incidence of amebiasis in the South which according to Craig<sup>85</sup> is only about three times greater. Reports on the incidence of amebiasis in the two regions convincingly demonstrate this fact. Wenrich, Stabler, and Arnett<sup>390</sup> found an incidence of 4.1 per cent of amebic infestation in routine stool examinations on 1,070 college freshmen at the University of Pennsylvania. Similar studies made by Faust and Headler<sup>119</sup> on 4,270 white clinic patients in New Orleans showed an incidence of 8.3 per cent. While the former incidence appears to be one-half as great as the latter it should be realized that college freshmen would be expected to be in better general health than clinic patients. In the authoritative opinions of Craig<sup>72</sup> and Faust<sup>118</sup> both incidences would be much higher if repeated stool examinations were made on each individual. As previously emphasized,<sup>277, 278, 282-284</sup> the relative frequency of amebiasis in the temperate climates is not thoroughly appreciated and consequently the possibility of amebic hepatic abscess is likely not to be considered. In this connection the surprisingly low incidence of amebic hepatic abscess to all liver abscesses recently reported at the Mayo Clinic is of further interest.<sup>34, 106</sup> Only 18 (or 14 per cent) of 125 surgical cases of liver abscess were attributable to ameba,<sup>106</sup> which is in striking contrast with the incidence of 63 per cent amebic hepatic abscess in our series of 287 liver abscesses (Graph I). Surveys made in both areas demonstrate clearly that these contrasting incidences (14 per cent at the Mayo Clinic and 63 per cent in the New Orleans series) cannot be explained solely by the respective incidences of amebiasis in the two regions. Thus, in a total number of 7,302 patients at the Mayo Clinic in which stool examinations were made *E. histolytica* was found in 1,275 (or 17.4 per cent),<sup>138, 228, 338, 347</sup> whereas similar studies on 4,270

white patients in New Orleans showed the incidence to be 8.3 per cent.<sup>119</sup> Faust<sup>117</sup> was also struck by "unexplained discrepancies in different population groups in the same locality." Referring to the incidence of amebiasis according to various surveys he states that, "Clinic patients in Philadelphia have been reported to have an incidence of only 1.1 per cent and college students in the same city 4.1 per cent, food handlers in San Francisco have been found to have only 3.0 per cent infection but University of California students, 53.0 per cent."

The sex factor apparently plays a definite role in the development of amebic hepatitis and hepatic abscess but its exact significance is not clearly understood. Its etiologic importance, however, is demonstrated by the fact that in a series of 1789 cases collected from the literature,<sup>413</sup> 1703 (or 95.1 per cent) were males. In our series of 181 cases there were 157 (or 86.7 per cent) males (Graph III). Rolleston and McNee<sup>330</sup> have attempted to explain this curious susceptibility in the male by the

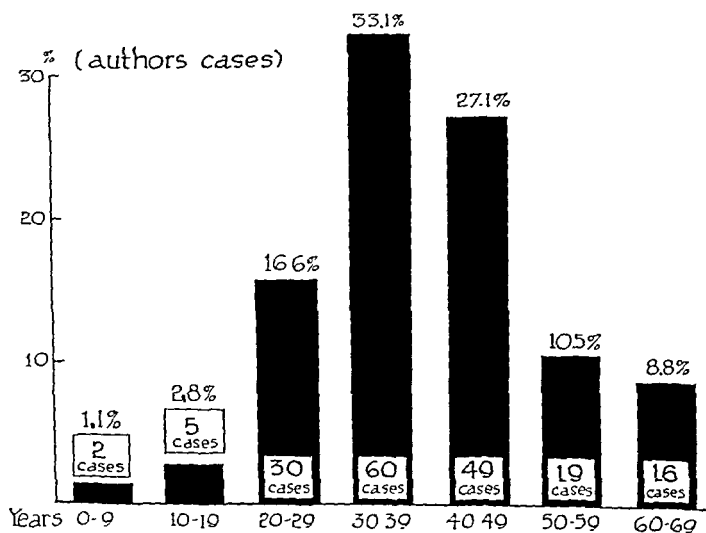


Graph III.—Sex incidence in amebic hepatic abscess based upon 1789 collected cases and 181 cases of the authors.

greater likelihood of trauma and the greater incidence of alcoholism which predispose to hepatitis in this sex. As previously stated, however, a more probable explanation of the preponderance of the male sex in amebic hepatic abscess is the predominant occurrence of intestinal amebiasis in the male. This is demonstrated by Manson-Bahr's<sup>237</sup> recent report of 535 cases of amebic dysentery in which the incidence of males was 83.9 per cent. However, the much higher incidence of intestinal amebiasis in males is yet to be satisfactorily explained.

Amebic hepatitis or hepatic abscess occurs principally during adult life or in the most active period and few cases are observed in individuals less than 20 or greater than 50 years of age. Of almost 400 cases

analyzed by Rogers and Megaw<sup>329</sup> 70 per cent occurred in the third and fourth decades. Ludlow,<sup>218</sup> Craig,<sup>85</sup> and Spittel<sup>353</sup> have reported similar incidences. Palazuelos and Lerner,<sup>292</sup> in an analysis of 74 cases, found that 35.6 per cent occurred in the third decade, 31.5 per cent in the fourth, and 17.8 per cent in the fifth. Whereas its occurrence is rare in children, it has been observed even in infants. In 1824, Brown,<sup>32</sup> although not cognizant of the etiology, observed a case in a 1-year-old negro girl who had a liver abscess following dysentery. Niblock<sup>268</sup> reported a case in a Hindu boy 11 months of age, and Leroy des Barres<sup>209</sup> recorded a case in an eight-month-old infant. Amebic dysentery also occurs rarely in children but as stated by Craig,<sup>85</sup> this is "not believed to be due to any inherent insusceptibility to the infection but to a lesser chance of contracting the infection." In our series of 181 cases the youngest patient was 6 years old, the oldest was 70, and the average age was about 40. The greatest age incidence according to decades was in the fourth and fifth, over 60 per cent of the cases occurring between the ages of 30 and 50 years and almost nine-tenths of the cases occurring between the ages of 20 and 60 years (Graph IV). Thus, our patients



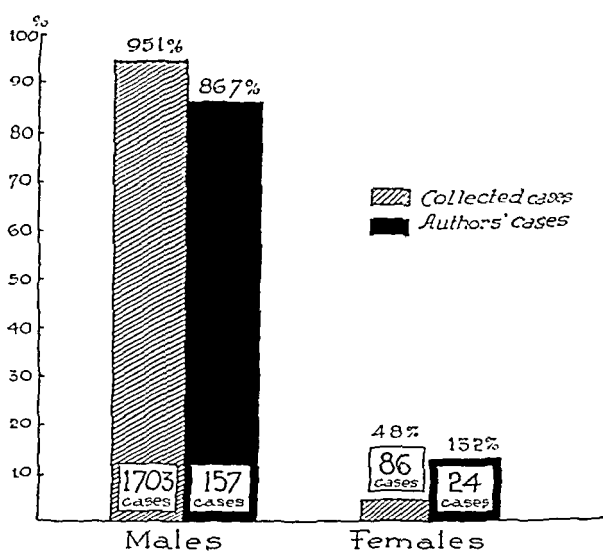
Graph IV.—Age incidence in amebic hepatic abscess according to decades in 181 cases of the authors.

are approximately a decade older than the tropical ones. As previously stated, this is probably due to the greater span of life in the tropics than in the temperate zones.

Whereas all races are apparently susceptible to infection with *E. histolytica* it is the consensus that in the tropics the natives suffer less with clinical manifestations, especially amebic dysentery, than white people. Moreover, a number of observers in the tropics have expressed the opinion that Europeans are more susceptible to the development

white patients in New Orleans showed the incidence to be 8.3 per cent.<sup>119</sup> Faust<sup>117</sup> was also struck by "unexplained discrepancies in different population groups in the same locality." Referring to the incidence of amebiasis according to various surveys he states that, "Clinic patients in Philadelphia have been reported to have an incidence of only 1.1 per cent and college students in the same city 4.1 per cent, food handlers in San Francisco have been found to have only 3.0 per cent infection but University of California students, 53.0 per cent."

The sex factor apparently plays a definite role in the development of amebic hepatitis and hepatic abscess but its exact significance is not clearly understood. Its etiologic importance, however, is demonstrated by the fact that in a series of 1789 cases collected from the literature,<sup>112</sup> 1703 (or 95.1 per cent) were males. In our series of 181 cases there were 157 (or 86.7 per cent) males (Graph III). Rolleston and McNee<sup>320</sup> have attempted to explain this curious susceptibility in the male by the



Graph III.—Sex incidence in amebic hepatic abscess based upon 1789 collected cases and 181 cases of the authors.

greater likelihood of trauma and the greater incidence of alcoholism which predispose to hepatitis in this sex. As previously stated, however, a more probable explanation of the preponderance of the male sex in amebic hepatic abscess is the predominant occurrence of intestinal amebiasis in the male. This is demonstrated by Manson-Bahr's<sup>237</sup> recent report of 535 cases of amebic dysentery in which the incidence of males was 83.9 per cent. However, the much higher incidence of intestinal amebiasis in males is yet to be satisfactorily explained.

Amebic hepatitis or hepatic abscess occurs principally during adult life or in the most active period and few cases are observed in individuals less than 20 or greater than 50 years of age. Of almost 400 cases

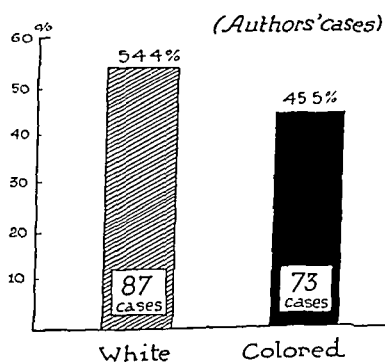
studies of the subject. A positive history of alcoholism was obtained by Waring<sup>386</sup> in 67.5 per cent of 40 cases, by Rogers<sup>320</sup> in 54.5 per cent of 44 cases, by Megaw<sup>342</sup> in 70 per cent of 170 cases, and by Chen and his associates<sup>55</sup> in 67.7 per cent of 31 cases. On the other hand Eolian<sup>112</sup> is of the opinion that alcoholism has little or no predisposing influence because the incidence of amebic hepatic abscess is no greater among the natives of Armenia whose habits are far from abstemious in this regard than among the Europeans. This is supported further by the relatively low incidence of alcoholism found in the investigations of other observers. Thus, a positive history of alcoholism was obtained by Peiris<sup>302</sup> in 24 per cent of 28 cases, and by Jayasuriya<sup>188</sup> in only 18 per cent of 73 cases. Unfortunately, the significance of the alcoholic factor cannot be ascertained in our series because in only 10 cases was any statement made concerning its consumption. Of this number 3 gave a positive history and 7 were abstainers.

The significance of seasonal influence upon the development of amebic hepatic abscess is questionable. In an analysis of 236 cases according to the four seasons, Rogers<sup>320</sup> found the incidence almost equal. Rolleston and McNee,<sup>330</sup> however, have expressed the opinion that sudden variations in temperatures are important factors, and Sehrumpf-Pierron<sup>340</sup> stated that the sudden occurrence of hot winds in Egypt was the most important cause of recurrence of amebic hepatitis. Whereas climatic factors cannot be considered definitely influential in the development of amebic hepatic abscess, a more definite relationship seems to exist regarding the incidence of amebic dysentery. According to Craig,<sup>85</sup> amebic dysentery occurs more frequently in hot, moist climates and is due probably to the increased possibility of transmission and to the depressing effect upon the resistance of the host.

*Pathogenesis.*—It has been clearly established by clinical as well as experimental investigations that amebic hepatitis is the result of invasion of the liver by the ameba. The three possible routes by which amebae may gain access to the liver are (1) by direct extension through the bowel wall, peritoneal cavity, and the capsule of the liver; (2) by the lymphatic route; and (3) through the portal vein. Councilman and Lafleur<sup>70</sup> originally contended that amebae "reach the liver by another route than through the blood and lymphatic vessels," that is, "by means of the abdominal cavity"; this was based upon their observations that the most frequent sites of these hepatic abscesses were in the periphery, either on the diaphragmatic or colonic surfaces of the right lobe, and the presence in one case of an associated amebic peritonitis in the right abdominal quadrant. The presence of amebae in the peritoneal exudate and in abscess beneath the right rectus muscle lends credence to this theory.<sup>362</sup> Extension through the lymphatics is based upon the finding of amebae in lymphatic vessels of the colon.<sup>50</sup> However, this mode of transmission is obviously rare, and is probably never operative.



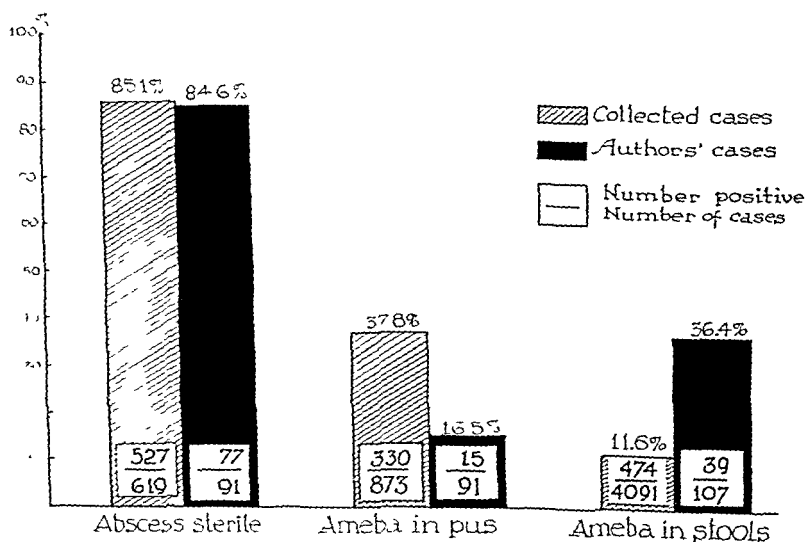
of amebic hepatic abscess than natives. Of 568 cases analyzed by Buchanan,<sup>35</sup> 75.8 per cent were white patients and 24.1 per cent natives. Somewhat similar observations were made by Ludlow<sup>218</sup> in Korea, and Herriek<sup>163</sup> in the Canal Zone. On the other hand, in a series of 150 cases reviewed by Huard and Meyer-May,<sup>174</sup> 66 (or 44.4 per cent) were among the white inhabitants and 84 (55.5 per cent) among the natives in Tonkin. Craig<sup>85</sup> believes that the comparative mildness of amebic symptoms among natives in the tropics is "largely due to a partial immunity to the effects of the parasite acquired by constant infection since childhood." In our series of 182 cases, 108 were white and 74 were colored patients. However, only the Charity Hospital group of 160 patients in this series can be considered because colored patients are not admitted to the Touro Infirmary. In this series of 160 cases there were 87 (or 54.4 per cent) white and 73 (45.5 per cent) colored patients, a distribution commensurable with the general admissions to the hospital of the two races (Graph V). As previously stated, the relatively high incidence of colored patients in this group as compared to other reported series may be accounted for, probably, by the fact that only one other institution in New Orleans admits negro patients, and possibly by the fact that white patients are more likely to consider and attempt to obtain antiamebic therapy before admission to the hospital.



Graph V.—Race incidence of amebic hepatic abscess in 160 cases of the authors.

A number of other factors such as alcoholism, traumatism, exposure, improper diet, and lowered resistance have been considered to have some predisposing influence upon the development of amebic hepatitis and hepatic abscess. Of these, excessive indulgence in alcohol is believed by most authorities to be the most important. In fact some have cited the more abstemious habits of females as a significant factor in their comparative freedom from this complication. Rolleston and McNee<sup>330</sup> believe that even the moderate use of alcohol predisposes to amebic hepatitis, as demonstrated by the increased incidence of this complication in natives who are not total abstainers. A number of observers have directed attention to the relatively high incidence of alcoholism in their

strated with greatest frequency in the earlier stages of amebic hepatitis or in the marked necrotic tissue of early abscesses and are rarely found in the older abscesses with thick fibrotic capsules. Probably this accounts for the fact that amebae are so difficult to find in the contents of large amebic abscesses, especially when first opened, although several days later they may be found in the "pus."<sup>190</sup> According to MacCallum<sup>222</sup> this may be explained on the basis that amebae require oxygen, and after the abscess has been opened and exposed to the air amebae may readily appear in the draining material. There is considerable discrepancy among different observers concerning the incidence of amebae in the abscess contents. Whereas Rogers,<sup>325</sup> Futcher,<sup>132</sup> and Chen and co-workers<sup>35</sup> were able to demonstrate amebae in the contents of hepatic abscesses in 96.2 per cent, 99.1 per cent, and 65 per cent of their respective series, Okinschewitsch,<sup>289</sup> Bressot,<sup>30</sup> and Huard and Meyer-May,<sup>174</sup> found this incidence to be 12 per cent, 11.9 per cent, and 7.4 per cent respectively in their series of cases. In a series of 873 cases collected from the literature, amebae were demonstrable in the abscess contents in 330 (or 37.8 per cent)<sup>414</sup> (Graph VI). In our



Graph VI.—Respective incidences of sterile abscesses, ameba in pus, and ameba in stools in collected and authors' cases of amebic hepatic abscess.

series of 91 cases, in which the results of this examination were stated, there were only 15 (or 16.5 per cent) with positive findings (Graph VI). The unusually high incidence reported by Rogers,<sup>325</sup> Futcher,<sup>132</sup> and Chen and his associates<sup>35</sup> may be explained by the fact that scraping of the abscess wall was generally performed. In our cases this was rarely done.

Previously the role of pathogenic bacteria in the production of amebic hepatic abscess was a subject of considerable discussion. Whereas pyo-

That amebae reach the liver from the primary focus in the intestine through the portal vein is the consensus of most authorities. Amebae are frequently observed in the capillaries and vessels of the intestinal submucosa and in the portal tributaries. According to Rogers<sup>325</sup> if "amebae happen to reach some part of the liver in such numbers as to cause clotting of several contiguous small veins so as to interfere with the blood supply sufficiently to produce a small focal necrosis with consequent softening of the walls of the veins allowing escape of the amebae into the soft liver tissue, the commencement of an abscess results." Once this process begins, further spread of the organisms occurs along the open veins with further destruction of the liver parenchyma and extension of the cavity in concentric circles until a fibrous capsule surrounding the abscess develops.

In the development of amebic hepatitis and hepatic abscess the two factors which play prominent roles are: (1) the production by the amebae of intrahepatic portal thrombosis and infarction, and (2) the cytolytic activity of the ameba. That amebae lodge in the smaller portal radicles producing thrombosis with typical infarction and consequent focal necrosis has been convincingly demonstrated by experimental and clinical investigations.<sup>293, 314</sup> These appear characteristically in the portal triads and extend peripherally towards the capsule, thus paving the way for the cytolytic activity of the amebae to produce lysis and destruction of the involved liver parenchyma. In one of the autopsy cases studied by Palmer,<sup>293</sup> amebae were found in a thrombosed branch of the portal vein in the liver. According to Craig,<sup>85</sup> in the earliest stage of abscess formation "there is an area of capillary congestion surrounding an area composed of cytolyzed tissue cells in which may be seen red blood corpuscles, degenerated liver cells, a few leucocytes, connective tissue cells, and granular debris, with now and then a trophozoite of *E. histolytica* lying in a zone of completely cytolyzed material." Undoubtedly, in many instances this early process of amebic hepatitis does not progress further but heals by connective tissue replacement. That this is not an infrequent occurrence in amebiasis is clearly shown by the fact that sections of liver in cases of active intestinal amebiasis reveal generalized increase in portal connective tissue and focal scar tissue residues of healed small amebic abscesses.

According to this concept it becomes obvious that in the early phase of an amebic hepatitis a balance exists between regression toward healing by scar tissue replacement and progression towards suppuration and abscess formation. Probably the scale is upset by certain predisposing factors such as the relative resistance of the host and virulence and number of the organisms, the presence of pathogenic bacteria, and possibly alcohol, trauma, and other detrimental agencies, resulting in true abscess formation.

The amebae are found characteristically in the zone of necrotic tissue adjacent to the outer dense fibrotic abscess wall. They can be demon-

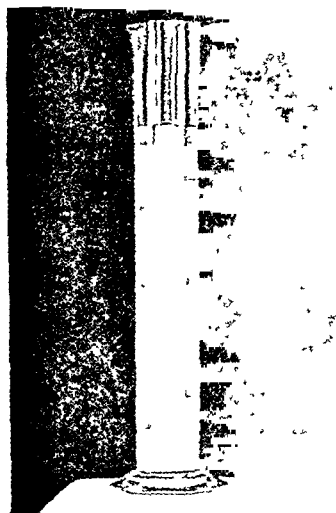


FIG. 1.—Colored photograph showing characteristic chocolate-sauce pus obtained from amebic abscess of liver (Case 3).

genic organisms undoubtedly produce hepatic abscesses, in cases of amebic abscess in which they are demonstrable they are probably secondary invaders and usually there is a change in character of the abscess contents. As has been previously emphasized, the fact remains that true amebic hepatic abscesses are characteristically bacteriologically sterile. Relatively large series of cases have been studied by Manson-Bahr,<sup>234</sup> Fitcher,<sup>132</sup> and Rogers,<sup>325</sup> who found the "pus" sterile in 91.1 per cent, 86.6 per cent, and 86.2 per cent respectively. In a collected series of 619 cases 527 (or 85.1 per cent) were found to be sterile<sup>415</sup> (Graph VI). An almost similar incidence (84.6 per cent) was found in our series of 91 cases (Graph VI). As previously emphasized,<sup>277-279, 282-285, 287</sup> this is an extremely important fact the significance of which will be better appreciated in the discussion of therapy. The pyogenic organisms most commonly found in secondarily infected amebic hepatic abscesses are streptococci and staphylococci. However, occasionally other forms are observed. Enterococci, *Bacillus coli*, and pneumococci have been reported by Huard and Mayer-May.<sup>174</sup> Of the 14 cases in our series in which secondary infection was present, staphylococci were demonstrable in 8, streptococci in 4, the combination of these two in 1, and *B. coli* in 1.

*Pathology.*—There is considerable variation in the gross appearance of the liver in amebic abscess depending upon the location and the degree and stage of involvement. Usually the liver is enlarged although if the abscesses are small and deeply situated it may have a fairly normal external appearance. On the other hand localized peritonitis with fibrinous exudation is usually present on the surface in those cases in which the abscess lies near the capsule. Adhesions to the diaphragm are present in those peripherally located abscesses in the dome of the liver.

When the liver is sectioned the abscesses become readily visible and the surrounding parenchyma presents evidence of fatty degeneration and venous congestion. Depending upon the stage of the process macroscopically the abscesses vary in size and character. Upon this basis Councilman and Lefleur<sup>70</sup> classified amebic abscesses into three types: (1) the small, which are acute; (2) the larger abscesses with partially fibrous walls; and (3) the chronic with hard, dense fibrous shells. The earliest visible stage of abscess formation appears as a minute grayish-brown area having a moth-eaten appearance and, according to Craig,<sup>83</sup> represents necrosis of cytotoxicity of tissue produced by the ameba. From this stage abscesses may be observed ranging in size from a few millimeters in diameter to 15 or 20 cm. Occasionally the abscess actually occupies almost the entire lobe of the liver.

Whereas the contents of the abscess have a characteristic appearance, there may be some variation depending upon the stage and nature of the infection. Thus, in the earlier stages of the nonsecondarily infected amebic abscesses the material has a viscid, glary semitransparent appear-

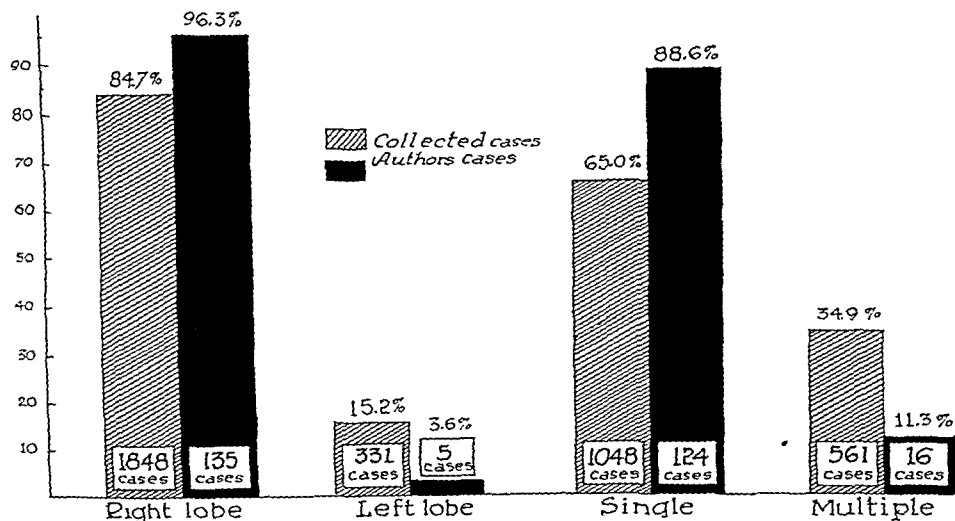
ance. Later the contents become less viscid and due to the mixture of blood assume yellowish-red or chocolate-brown color (Fig. 1). This characteristic appearance of the material contained in the abscess has been variously described as resembling "liver scrapings" (*raclure de foie*),<sup>127</sup> "crushed strawberries" (*fraise écrasée*),<sup>45</sup> "wine dregs" (*lie de vin*),<sup>206</sup> anchovy sauce, and "chocolate sauce" which in our opinion<sup>277</sup> is the most descriptive (Fig. 1). According to Costantini<sup>68</sup> and Manson-Bahr<sup>234</sup> this material is so characteristic of an amebic hepatic abscess that its presence justified a positive diagnosis even though amebae are not demonstrable. Once the abscess becomes secondarily infected the contents become more purulent and develop a greenish or grayish-yellow creamy character. However, it should be realized that the contents of a pure amebic abscess do not consist of pus but a mixture of blood, cytolyzed liver tissue, and small solid particles of liver parenchyma which have resisted destruction.

The stage of the lesion also determines the character of the abscess wall. Thus, in the earlier stages of abscess formation the wall may be scarcely visible, whereas in the later stages a dense well-defined fibrous tissue capsule of varying thickness is conspicuously present. According to Craig<sup>85</sup> this typical fibrous wall is "due to the fact that the connective tissue of the liver offers a marked resistance to cytolysis and that the invasion of tissue of this parasite stimulates connective tissue formation." The importance of this limiting fibrous membrane is emphasized by Rogers<sup>325</sup> who believes that once it has formed, further destruction of liver tissue occurs only after secondary infection develops. In medium-sized abscesses the inner aspect of the fibrous wall has a typical shaggy appearance and is covered with shreds of necrotic tissue. This is due to the connective tissue framework of the liver parenchyma which resists the cytolytic activity of the ameba. Cases in which the bands or "shreds of partly cytolyzed connective tissue reach entirely across the abscess cavity" have been described by Craig.<sup>85</sup> The internal surface of the fibrous wall has a smoother appearance in older chronic abscesses.

The microscopic appearance of the abscess also varies according to the stage of the process. The lesion is essentially one of the colliquative necrosis and liver parenchymal disintegration with characteristic absence of leucocytic infiltration and inflammatory reaction. In the early stages of amebic hepatitis, section reveals cytolyzed and degenerated liver cells, red blood cells, a few leucocytes and fibroblasts and an occasional ameba surrounded by a zone of capillary congestion. As the lesion advances to true abscess formation a well-defined wall of connective tissue appears surrounding the cavity containing granular necrotic liver tissue, erythrocytes, lymphocytes, and a few polymorphonuclear leucocytes. In the more peripheral areas of the abscess wall, amebae can frequently be observed invading the surrounding liver parenchyma. In the older thick-walled abscesses there is present cytolyzed necrotic tissue contain-



Faust,<sup>116</sup> who recently analyzed 249 autopsy cases from the Gorgas Hospital in Panama and the Charity Hospital in New Orleans, found that the cecum and appendix were the most frequent sites of involvement. Accordingly, the right half of the colon would seem to be the greatest source of amebic infection. On the basis of the two currents of blood in the portal vein this area drains into the right lobe of the liver and consequently there is greater likelihood of amebic localization in this lobe.



Graph VII.—Relative incidence of amebic hepatic abscess according to location and multiplicity of lesions in collected and authors' cases.

Whereas clinically amebic hepatic abscess has been considered characteristically single rather than multiple, varying incidences have been reported depending largely upon analyses of clinical or autopsy cases. Single abscesses were reported by Davidson<sup>94</sup> in 75 per cent, two abscesses in 11 per cent, and more than two in 14 per cent. In analyses of autopsy cases the respective incidences of multiple abscesses found by Gaide,<sup>134</sup> Craig,<sup>75</sup> Sambuc,<sup>337</sup> and Mondon<sup>255</sup> were 30, 60.8, 64.8 and 66 per cent. Further demonstration of the significance of clinical and post-mortem studies on the incidence of single and multiple abscesses is furnished by the studies of Huard and Meyer-May.<sup>174</sup> Whereas in a series of 150 clinical cases multiple abscesses were found in only 13 (or 8.6 per cent), in a series of 43 autopsy cases multiple abscesses were observed in 31 (or 72 per cent). As previously stated the obvious explanation for such discrepancies lies in the fact that autopsy cases are likely to have more extensive involvement and permit more thorough examination than clinical cases. In a collected series of 1,609 cases, a single abscess was present in 1,048 (or 65 per cent) and multiple abscesses in 561 (or 34.9 per cent) (Graph VII).<sup>417</sup> In our series of 140 cases these respective figures were 124 (or 88.6 per cent) and 16 (or

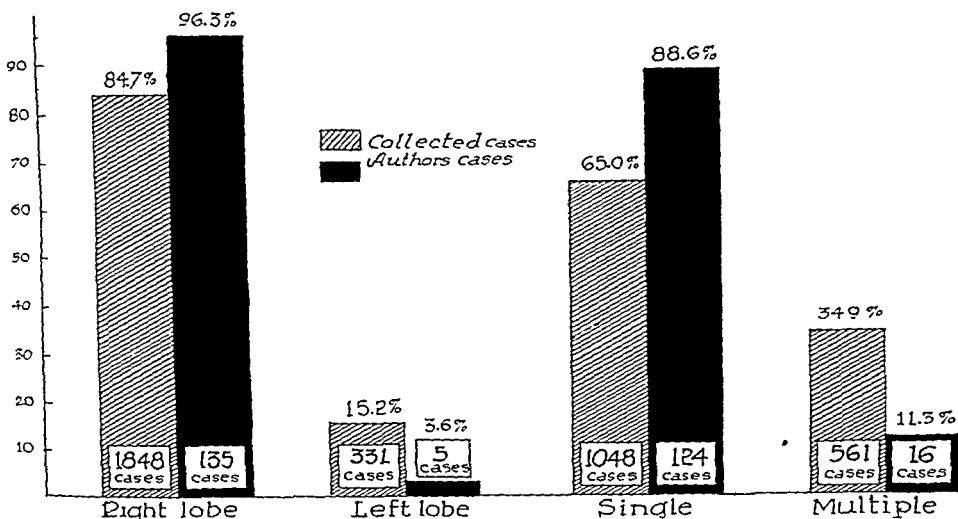


ing fibrin, erythrocytes and monocytes on the inner aspect, and proliferating fibroblasts and lymphocytes near the periphery extending into an area of hyperemia. Calcification of an amebic hepatic abscess is considered most unusual.<sup>180</sup>

Whereas the location and number of amebic hepatic abscesses may be variable, characteristically they are single and occur in the right lobe near the dome of the liver or the inferior surface near the hepatic flexure of the colon. The incidence of right and left lobe involvement and single and multiple abscesses varies according to different authors but depends essentially upon analyses based upon clinical or autopsy cases. Fontan<sup>127</sup> recorded right lobe involvement in 97 per cent of his cases. In their analysis of 150 cases, Huard and Meyer-May<sup>175</sup> found right lobe abscesses in 92 per cent and Moynihan<sup>259</sup> observed an incidence of 71 per cent in this lobe and 16 per cent in the left. Clark,<sup>63</sup> in a study of 95 autopsy cases, found an incidence of 55.7 per cent in the right lobe, 8.4 per cent in the left lobe, 16.8 per cent in the right and left lobes, and 15.7 per cent in all lobes. Left lobe involvement occurs so infrequently that it is considered report-worthy.<sup>149</sup> In a collected series of 2,179 cases the right lobe was involved in 1,848 (or 84.7 per cent) and the left lobe in 331 (or 15.2 per cent)<sup>416</sup> (Graph VII). In our series of 140 cases these respective incidences were 96.3 and 3.6 per cent (Graph VII). Probably the explanation for the higher incidence of right lobe involvement in our series lies in the fact that a large number of autopsy cases are included in the collected series. In previous publications attention was directed to this fact and collected clinical cases revealed a higher incidence of right lobe involvement in the latter and a five times greater incidence of bilateral involvement in the former. Obviously, fatal cases coming to autopsy are more likely to have extensive liver involvement. Moreover, in the clinically observed cases small abscesses may resolve and remain unrecognized under appropriate therapy, whereas thorough post-mortem examination will reveal even these small lesions.

In previous communications we expressed the opinion that predominance of right lobe involvement may be explained possibly on the basis of certain experimental investigations of Sérégé,<sup>341, 342</sup> Glenard,<sup>140</sup> Bartlett, Corper, and Long,<sup>14</sup> and Copher and Dick.<sup>65</sup> These investigators demonstrated the existence of two currents of blood in the portal vein, one from the superior mesenteric vein, which goes to the right lobe, and one from the inferior mesenteric and splenic veins, which goes to the left lobe of the liver. It has been shown by numerous observers that amebic lesions are encountered most frequently in the cecum and ascending colon.<sup>63, 74, 85, 116, 186, 398</sup> In almost two-thirds of 36 cases studied by Rogers<sup>325</sup> the lesions were actually limited to the cecum and ascending colon. In a detailed study of 186 cases, James<sup>156</sup> found that in those cases in which the ulceration was more or less localized the cecum was involved in 87.3 per cent and the ascending colon in 57.1 per cent.

Faust,<sup>116</sup> who recently analyzed 249 autopsy cases from the Gorgas Hospital in Panama and the Charity Hospital in New Orleans, found that the cecum and appendix were the most frequent sites of involvement. Accordingly, the right half of the colon would seem to be the greatest source of amebic infection. On the basis of the two currents of blood in the portal vein this area drains into the right lobe of the liver and consequently there is greater likelihood of amebic localization in this lobe.



Graph VII.—Relative incidence of amebic hepatic abscess according to location and multiplicity of lesions in collected and authors' cases.

Whereas clinically amebic hepatic abscess has been considered characteristically single rather than multiple, varying incidences have been reported depending largely upon analyses of clinical or autopsy cases. Single abscesses were reported by Davidson<sup>94</sup> in 75 per cent, two abscesses in 11 per cent, and more than two in 14 per cent. In analyses of autopsy cases the respective incidences of multiple abscesses found by Gaide,<sup>134</sup> Craig,<sup>75</sup> Sambue,<sup>337</sup> and Mondon<sup>255</sup> were 30, 60.8, 64.8 and 66 per cent. Further demonstration of the significance of clinical and post-mortem studies on the incidence of single and multiple abscesses is furnished by the studies of Huard and Meyer-May.<sup>174</sup> Whereas in a series of 150 clinical cases multiple abscesses were found in only 13 (or 8.6 per cent), in a series of 43 autopsy cases multiple abscesses were observed in 31 (or 72 per cent). As previously stated the obvious explanation for such discrepancies lies in the fact that autopsy cases are likely to have more extensive involvement and permit more thorough examination than clinical cases. In a collected series of 1,609 cases, a single abscess was present in 1,048 (or 65 per cent) and multiple abscesses in 561 (or 34.9 per cent) (Graph VII).<sup>417</sup> In our series of 140 cases these respective figures were 124 (or 88.6 per cent) and 16 (or

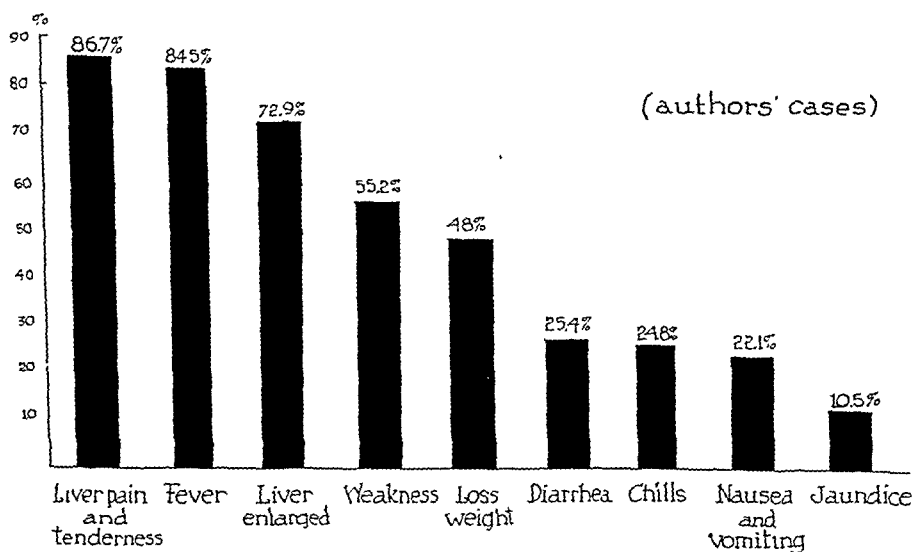
11.3 per cent) (Graph VII). The higher incidence of single abscesses in our series as compared with the collected cases is undoubtedly due to the fact that the great majority of the former were clinical cases, whereas a large proportion of the latter included autopsy cases.

*Clinical Manifestations.*—The onset of amebic hepatitis or hepatic abscess varies considerably and may be acute, subacute, or insidious depending upon a number of factors such as the virulence of the infection, the resistance of the host, and others previously mentioned in etiology and pathogenesis. Clinical manifestations of this complication also may develop during or immediately following the stage of acute intestinal amebiasis, during active or quiescent periods of chronic intestinal amebiasis, in healthy carriers, or in patients who have never had dysenteric manifestations of intestinal amebiasis. Usually clinical evidence of amebic hepatitis appears early in its development. However, it should be realized that occasionally this may not become apparent until extensive involvement of the liver has occurred.

The period elapsing between the dysenteric manifestations and the onset of liver involvement may vary considerably although it is usually from one to three months.<sup>85</sup> Moreover, during the interim a latent infection of the bowel cannot be definitely excluded. Cases have been recorded in which amebic hepatic abscess developed twenty, thirty, and even forty-three years after the dysenteric manifestations.<sup>194, 217, 231</sup> In some of our cases this period extended from six to eight years.

The importance of recognizing the early development of amebic hepatitis has been emphasized repeatedly.<sup>227-279, 282-285, 287, 329</sup> During this early period or presuppurative stage<sup>329</sup> there is invasion of the liver by amebae but true abscess formation has not yet occurred. The obvious significance of recognizing this period lies in the fact that the institution of appropriate therapy may prevent progression to abscess formation. This is exemplified by Case I reported in this communication. According to Rogers and Megaw<sup>329</sup> the onset during this stage may be considered as acute or chronic. In the former the clinical manifestations are readily evident, quite pronounced, and develop rapidly, whereas in the latter they are much less distinctive and develop more gradually. Determinations of the relative frequency of each type of onset in our series were made by arbitrarily considering cases in which symptoms had clearly developed over a period of three weeks or less, as acute, and those in which the duration was longer, as chronic. Accordingly, in the series of 181 cases, 68 (or 37.6 per cent) were acute and 113 (or 62.3 per cent) were chronic. In the acute group the shortest duration was one day and the average was from ten days to about two weeks. In the chronic group the longest duration was three years and the average from three to six months. Wijerama<sup>394</sup> found in his series of 48 cases that the duration of symptoms was from three days to six months with an average of four weeks.

The clinical manifestations of amebic hepatitis and hepatic abscess may be divided into two groups: (1) systemic, and (2) local. Fever is undoubtedly the most frequent systemic manifestation. Manson-Bahr<sup>234</sup> reported the presence of fever in 85 per cent of a series of 45 cases. In Wijerama's<sup>394</sup> series of 48 cases fever was present in 87 per cent. Palazuelos and Lerner<sup>292</sup> record an incidence of 89 per cent in their series of 74 cases. In our series of 181 cases, fever was the most frequent systemic manifestation, being present in 153 (or 84.5 per cent) cases (Graph VIII). There is some variation in the character and degree of pyrexia depending upon the type of onset and the presence or absence of secondary infection and other complications. Rogers<sup>328</sup> states that in the acute forms fever is high and intermittent or remittent in character, whereas in the chronic types it may even be absent. In our series all the cases in which fever was absent were of the chronic variety.



Graph VIII.—Relative incidence of various clinical manifestations in amebic hepatitis and hepatic abscess based upon analysis of 181 cases of authors.

Sambue<sup>337</sup> states that in 60 per cent of the cases the temperature is below 38.5° C. According to Chen and co-workers<sup>55</sup> most of their patients had no fever on admission and the average temperature was 37.3° C. Characteristically fever is of a low grade and intermittent in character (Figs. 4, 7, 10, and 17). Definite hyperpyrexia which is septic in type usually indicates secondary infection. The majority of cases in our series were of the former type and only a few fell into the latter category.

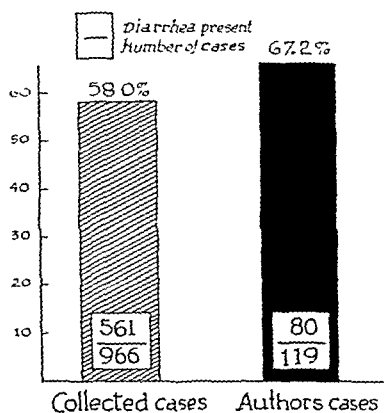
In order of frequency other systemic manifestations are weakness, loss of weight, anorexia, diarrhea, chills and profuse perspiration, nausea and vomiting, sallowness and jaundice (Graph VIII). Obviously the incidence and prominence of these manifestations depend largely upon the extent of hepatic involvement and the development of sec-

ondary infection. Weakness and loss of weight are present in a large proportion of cases and may be pronounced in chronic extensive abscesses. Definite complaints of weakness and loss of weight were found in 55.2 per cent and 48 per cent respectively in our series (Graph VIII). In the more extensive abscesses loss of as much as forty to sixty pounds was recorded. Anorexia, nausea, and vomiting are not infrequently observed, especially in the early stages. In chronic abscesses nausea and vomiting are usually not prominent, and in our series were observed in only 22.1 per cent of the cases (Graph VIII). Chills and profuse perspiration are also not common in the chronic abscesses but are more likely to occur in the acute and subacute forms and those associated with remittent fever. Young<sup>403</sup> reported chills occurring in an incidence of 73.3 per cent in his series of cases but Manson-Bahr<sup>234</sup> found this present in only 4.4 per cent and Peiris<sup>302</sup> stated that profuse sweats were distinctly uncommon. In a previous publication<sup>277</sup> the incidence of chills in a collected series was found to be 24.7 per cent. In our series of 181 cases they were recorded in 24.8 per cent (Graph VII).

According to some observers a peculiar sallowness or dirty yellowish tinge of the skin characteristically develops in amebic abscess of the liver. However, as previously stated, in our experience this is more likely to be encountered in chronic abscess of long duration and extensive involvement and cannot be considered as characteristic of amebic abscess because it is merely an associated manifestation of conditions producing cachexia and emaciation. Actual jaundice occurs relatively infrequently and when deep is indicative of hepatic destruction. In their critical analysis of this subject, Patino Mayer and Pataro<sup>299</sup> state that while jaundice may be due to compression of the bile radicles by enlargement of the abscess, this is relatively rare and the condition should be most commonly interpreted as an amebic hepatitis. The incidence and degree of jaundice vary according to different reports. Rolleston<sup>330</sup> states that it is usually not pronounced and consists merely of a tinging of the sclera; whereas Young<sup>403</sup> found it present in a third of his cases and Palazuelos and Lerner<sup>202</sup> observed a subicteric tinge in 27 per cent of their cases, Ludlow<sup>218</sup> records an incidence of only 3 to 4 per cent, and Peiris<sup>302</sup> and Jayasuriya<sup>188</sup> report an incidence of about 4 and 6 per cent, respectively. Others<sup>250, 251</sup> have reported incidences of about 10 per cent. In our series jaundice occurred in 10.5 per cent and the icterus index varied from the highest figure of 200 to the lowest of 5 with an average of about 38. Palazuelos and Lerner<sup>202</sup> found in their series of 74 cases that the van den Bergh was normal in 50 per cent, slightly increased in 34.6 per cent (6 to 20 mg. per cent), and definitely increased in 15.4 per cent (20 to 60 mg. per cent).

Unfortunately the fallacious impression still exists that diarrhea, whether as an antecedent or an accompanying manifestation, occurs with significant frequency in amebic hepatitis and hepatic abscess. This

may be explained to some extent by the fact that amebiasis and amebic dysentery are generally confused.<sup>65, 282, 283, 287</sup> As previously stated, it should be thoroughly realized that amebic hepatic involvement occurs in a relatively large number of patients who have never had a previous diarrhea. This is a particularly significant fact in the diagnostic consideration of amebic abscess of the liver and we have emphasized this repeatedly.<sup>277-279, 282, 283, 287</sup> An antecedent history of diarrhea was found in about 45 per cent of the series studied by Jayasuriya,<sup>188</sup> Peiris,<sup>202</sup> and Staffieri<sup>254</sup> and in about 60 per cent of those analyzed by Manson-Bahr,<sup>254</sup> Murray,<sup>259a</sup> and Thurston.<sup>373</sup> In a series of 966 cases collected from the literature only 561 (or 58 per cent) or a little more than one-half had a positive history of antecedent diarrhea<sup>418</sup> (Graph IX). In our series this incidence was 67.2 per cent and the diarrhea was a symptom at the time of admission to the hospital in only 25.4 per cent (Graph IX). Thus, in from one-third to almost one-half the



Graph IX.—Incidence of history of diarrhea in amebic hepatic abscess.

cases history of an antecedent diarrhea will not be obtained. This is explained on certain anatomicopathologic features of amebic infections. On the basis of clinical<sup>13, 84, 103, 262, 371, 398</sup> as well as experimental<sup>187, 192, 196</sup> observations it has been clearly established that amebic infection of the large bowel may exist in the absence of dysenteric manifestations. Such manifestations occur most commonly in rectal amebiasis but as stated above it has been shown by numerous observers that amebic lesions are encountered most frequently in the cecum and ascending colon. Thus, the probable explanation for the relatively high incidence of amebic hepatitis in the absence of an antecedent diarrhea is based, as previously presented by us,<sup>95, 278, 287</sup> on the frequency of localization of amebic infections to the right half of the colon and the respective differences in function of the right and left halves of the colon. Relatively slight infections limited to the sigmoid and rectum produce irritation and excessive secretions of fluids with consequent dysenteric manifestations,

whereas similar lesions limited to the cecum and ascending colon do not cause diarrhea because the fluid is absorbed in its passage through the uninvolved and normally functioning left side of the colon. In complete accord with this explanation, Solier and Dejou<sup>350</sup> recently reported a case in which autopsy studies were made and which exemplified this concept.

Probably the earliest and most constantly encountered local manifestations of amebic hepatitis are pain and tenderness in the region of the liver. The frequency of localized pain and tenderness is revealed by the fact that various observers have reported its incidence in from 75 to almost 100 per cent.<sup>419</sup> In our series these were the most constant manifestations having an incidence of 86.7 per cent (Graph VIII). Varying in character from a dull aching discomfort to a severe sharp pain it is usually located directly over the liver, although it may be most pronounced immediately below the right anterior costal margin, in the epigastrium, about the ninth interspace in the axillary line, or posteriorly over the twelfth rib. Not infrequently radiation to the shoulder, usually the right, is a prominent complaint and may be explained on the basis of diaphragmatic irritation. Its significance has been emphasized by Manson-Bahr<sup>234</sup> who found it present in 44.4 per cent on the right and in 4.4 per cent on the left. In the latter, abscesses of the left lobe were present. On the other hand shoulder pain was present in only about one-sixth of Manson's<sup>232</sup> series, one-fifth of Jayasuriya's<sup>188</sup> series, and about one-twentieth of Huard and Meyer-May's series.<sup>174</sup> Similarly, in our cases shoulder pain was recorded in 16.6 per cent. Ludlow<sup>218</sup> has described a sign which he considers of diagnostic significance and consists of a deep-seated pain produced by a sudden thrust of the end of the finger on the liver. The most common point at which this can be elicited is about two inches below the right costal margin. Boccia<sup>24</sup> has observed subxiphoid tenderness (Castellani's sign) as a significant manifestation in amebic hepatitis.

The next most constant local manifestation of amebic hepatitis and hepatic abscess is enlargement of the liver. Whereas, it may not be obvious on physical examination, most experienced observers agree that a varying degree of hepatomegaly is almost invariably present. Different observers have reported incidence of hepatomegaly varying from 64 to 100 per cent.<sup>234, 292, 366, 394, 403</sup> In our series of 181 cases, the liver was clinically enlarged in 72.9 per cent (Graph VIII). Manifestations of liver enlargement are sometimes apparent by widening of the lower right intercostal spaces with some restriction of respiratory movement on this side and possibly some dilatation of the superficial veins. Usually the liver margin can be palpated below the right costal arch anteriorly and on percussion liver dullness will be found to extend higher than normal, especially in the mid- or posterior axillary line. Frequently tenderness and some rigidity of the abdominal muscles in the upper right quadrant can be elicited. Occasionally there may be observed in

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this area a distinct localized bulging with redness and edema of the skin indicating involvement of the abdominal parietes.<sup>351</sup> Associated diaphragmatic pleurisy and basal lung changes on the right side are not uncommon and are due not only to compression of the lower portion of the right lung but also to contiguous inflammatory involvement. Such disturbances are manifested by localized pain especially on deep inspiration, a hacking nonproductive cough, dullness, diminished breath sounds, crepitant râles, and a friction rub. In some there may be signs of fluid in the pleural cavity. Such signs occur with varying frequency and obviously depend upon the extent of hepatic involvement. Wijerama<sup>394</sup> reported such findings in a third of the cases and Jayasuriya<sup>188</sup> in slightly over one-half.

*Laboratory Findings.*—The most informative laboratory procedures in amebic hepatitis and hepatic abscess are certain blood studies, stool examination, and roentgenography. Of the blood studies the leucocyte count is probably the most significant. Various observers<sup>95, 238, 277-279, 282-287, 328</sup> have directed attention to the moderate leucocytosis in amebic hepatitis and hepatic abscess as contrasted with the pronounced leucocytosis occurring in the pyogenic forms. Moreover, in the former, characteristically there is not a concomitant increase in polymorphonuclear leucocytes. In their group of cases, Manson-Bahr and Willoughby<sup>238</sup> found that the highest leucocyte count was 25,000, the lowest 7,500, and the average 15,000 with no eosinophilia. They also observed that the lowest counts were associated with the largest abscess cavities. In their series of 150 cases, Huard and Meyer-May<sup>172, 177</sup> found the leucocyte count to be between 10,000 and 16,000 in one-half of the cases and between 8,000 and 10,000 in the other half. In his study of 73 cases, Jayasuriya<sup>188</sup> found the leucocyte count to vary between 10,000 and 30,000 with an average polymorphonuclear percentage of 69. Wijerama<sup>394</sup> recorded counts between 8,000 and 32,000 with an average of 12,000 and an average polymorphonuclear percentage of 72. These respective figures in the series studied by Palazuelos and Lerner<sup>292</sup> were 2700, 29,000, 12,500, and 74.1 per cent. In our series these findings are summarized in Table I. Accordingly, it may be observed that variations in the leucocyte count apparently depend upon the chronicity of the process. Thus, while the average leucocyte count was 16,460 in the acute forms, it was somewhat less than 13,000 in the chronic type. It may be stated that in general as the lesion becomes more chronic the leucocyte count diminishes. Rogers<sup>327</sup> has expressed the opinion that high leucocytosis indicates multiple abscesses and a bad prognosis. In our experience a pronounced leucocytosis usually indicates secondary bacterial invasion, an observation which Wright<sup>299</sup> has also recently observed. This may be illustrated to some extent by the contrasting leucocyte counts in the amebic and pyogenic hepatic abscesses that we have studied.<sup>286, 287</sup> Thus, the average leucocyte count in acute pyogenic hepatic abscesses was found to be 26,924 whereas in amebic abscesses



TABLE I  
BLOOD PICTURE IN AMEBIC HEPATIC ABSCESS\*

	ACUTE	CHRONIC	TOTAL
Leucocytes:			
Lowest	7,500	2,000	2,000
Highest	31,500	23,000	31,500
Average	16,460	12,700	14,300
Neutrophils:			
Lowest	60%	59%	59%
Highest	97%	95%	97%
Average	79%	75%	78%
Hemoglobin:			
Lowest	50%	30%	30%
Highest	90%	90%	90%
Average	72%	60%	66%
Erythrocytes:			
Lowest	2,650,000	1,950,000	1,950,000
Highest	4,975,000	4,800,000	4,975,000
Average	3,872,000	3,490,000	3,670,000

\*Based on analysis of authors' cases.

the corresponding figure was 16,460. The eosinophile count in amebic hepatic abscess was not found significant. An associated secondary anemia is present in the majority of cases and is more pronounced in the chronic forms. Thus, the average hemoglobin percentage was 72 in the acute cases and 60 in the chronic, while the average erythrocyte count was 3,872,000 in the former and 3,490,000 in the latter.

In 1927, Craig<sup>78</sup> demonstrated the presence of specific complement-fixing properties for *E. histolytica* in the blood sera of persons harboring this parasite and thus established the basis for the complement fixation test. Subsequent investigators<sup>120</sup> fully confirmed the meritorious investigations of Craig.<sup>79-82, 86-88</sup> The high degree of specificity that has been demonstrated with this test and the results that have been obtained clearly indicate its usefulness as a diagnostic laboratory procedure in questionable cases of amebiasis and especially in amebic hepatitis and hepatic abscess. The technique which is similar to the standard complement fixation test for syphilis with appropriate modifications in the antigen has been described in a number of previous publications.<sup>121</sup> Unfortunately, the difficulty experienced in obtaining a potent antigen has greatly hindered the routine use of this test in the clinical laboratory. Accordingly, as stated by Faust,<sup>117</sup> "Until the preparation of *E. histolytica* antigen is simplified, it cannot become generally available for the clinical laboratory."

Examination of the stools for the presence of amebae is another important laboratory procedure although their incidence varies considerably according to different reports. Thus, Tao<sup>265</sup> records their presence in the stools in 77.7 per cent of his cases, whereas Manson-Bahr<sup>231</sup> found a positive incidence in only 4.4 per cent and Palazuelos and Lerner<sup>202</sup> in only 13.5 per cent. Chen and his associates<sup>77</sup> reported an incidence of 34.1 per cent and Wijerama,<sup>344</sup> 31.2 per cent. In a collected series<sup>122</sup> of 4,091 cases, amebae were reported present in the stools in 474 (or

11.6 per cent) and in our series of 107 cases in which the results of this examination were stated amebae were found in 39 (or 36.4 per cent) (Graph VI). As previously stated this incidence will undoubtedly be greatly influenced by the experience of the examiner, the technique employed, and the repetition of examination in each case.

Roentgenography is undoubtedly one of the most important and dependable diagnostic laboratory procedures in amebic hepatic abscess. Among the early investigators who recognized the significance of radiologic examination in amebic hepatic abscess are Loison,<sup>212</sup> Quadrome,<sup>312</sup> B  cl  re,<sup>17, 18</sup> and others.<sup>43, 164, 187, 210, 300</sup> Numerous observers have directed attention to the characteristic elevation and immobility of the diaphragm.<sup>99, 203, 295</sup> Accordingly, it is important to perform fluoroscopic examination of the patient in the upright position. Moreover, as emphasized by Pancoast,<sup>295</sup> the presence of lung reaction is of diagnostic significance and when present usually indicates an amebic infection because these abscesses occur most frequently on the convex surface of the liver in close contact with the diaphragm. The inestimable value of certain characteristic roentgenologic changes in amebic hepatic abscess and subdiaphragmatic suppuration has been repeatedly stressed by Granger<sup>144</sup> and by us.<sup>277-287</sup> In uncomplicated abscess of the liver, a distinct bulging of the diaphragm may be observed pointing upward into the lower lung field in both the anteroposterior (Figs. 2, 5, and 8) and lateral roentgenograms (Figs. 3, 6, 9, and 11). The presence of this picture is considered almost pathognomonic. Moreover, it is possible to distinguish subphrenic abscess complicating a liver abscess from that due to other causes. Thus, in the former there occurs characteristically an obliteration of the cardiophrenic angle in the anteroposterior roentgenogram (Figs. 2, 5, and 8), and obliteration of the anterior costophrenic angle in the lateral view (Figs. 3, 6, 9, and 11). On the other hand, in subphrenic abscess due to other causes obliteration of the costophrenic angle is present in the anteroposterior roentgenogram and the posterior costophrenic angle in the lateral view. Although abscesses of the left lobe of the liver occur relatively infrequently their presence has been difficult to demonstrate. For this reason the roentgenologic method described by Miles<sup>274</sup> is of distinct value. He has shown that abscesses in this lobe produce characteristic pressure deformities on the barium-filled stomach. The cardia and duodenal cap are displaced and the lesser curvature assumes a typical crescentic shape.

The inestimable value of roentgenography in the diagnosis of amebic hepatic abscess is clearly demonstrated by the reports of various observers. A positive diagnosis was obtained by Young and Bristow<sup>404</sup> in all of a series of 25 cases. Huard and Meyer-May<sup>174</sup> reported a positive diagnosis in 80 per cent of 70 cases and Palazuelos and Lerner<sup>292</sup> in 69 per cent of 74 cases. In our series, there were 150 cases in which roentgenologic studies were made with positive diagnosis in 132 (or 88 per cent).

Modifications in technique, presumably as aids in the roentgenologic diagnosis of liver abscess, have been suggested by a number of observers. Some have advocated aspiration of pus from the abscess cavity and the introduction of an iodized oil followed by roentgenologic studies.<sup>423</sup> Accordingly, the size, shape, and position of the abscess may be visualized better and its drainage and progress controlled more satisfactorily. In more recent communications a number of authors emphasize the value of this procedure.<sup>424</sup> A slight modification of this technique consists of injecting air in addition to a small amount of lipiodol and taking roentgenograms with the patient in various positions.<sup>41, 105</sup> Chung and his co-workers<sup>60</sup> believe that this permits better delineation of the abscess cavity. They studied 5 cases in this manner over a period of time and interpreted the continued presence of lipiodol in the liver for almost a year as indicating that the abscess had not yet completely healed. Accordingly they state that whereas the patient may appear clinically cured the loss of liver tissue consequent to the abscess is so great that it may require weeks or months to heal completely. Although this may be true, one wonders to what extent the presence of the lipiodol contributed to the prolongation of this period. Under these circumstances lipiodol is injected into a closed space and it is well known that lipiodol injected into a closed space in other parts of the body remains present for long periods of time. Sarmiento<sup>339</sup> has recently voiced his objection to this procedure on the basis that it is usually unnecessary and the possibility of secondary infection may even be dangerous. Whereas under certain circumstances the procedure may be of diagnostic value, in our opinion it should not be employed routinely. Hepatography is still another method advocated and employed by some observers for visualization of the abscess.<sup>36, 315, 401, 402</sup> This is done by the intravenous administration of thorium dioxide and the abscess appears on the roentgenogram as a negative shadow. As previously emphasized, this procedure appears unjustified in view of the present state of insufficient knowledge regarding the end effects of thorium dioxide, particularly in a condition which otherwise can be so readily diagnosed.<sup>277, 278, 287, 331</sup> In 1932, the Council on Pharmacy and Chemistry<sup>372</sup> directed attention to the possible deleterious effects of the intravenous administration of such a radioactive substance as thorium dioxide. Subsequently, the proclivity of this substance to produce damage to tissue was emphasized further by numerous clinical and experimental observations.<sup>107</sup>

*Diagnosis.*—The diagnosis of amebic hepatitis and hepatic abscess is not difficult if the conditions are kept in mind and the clinical manifestations and laboratory examinations accorded due consideration. An amebic hepatitis should always be considered in a patient presenting a low-grade daily remittent or intermittent fever, pain and tenderness over the liver area, moderate leucocytosis without a concomitant proportionate increase in polymorphonuclear leucocytes, and *E. histolytica* in the stools. Such a clinical picture during or shortly after an attack

of amebic dysentery more strongly indicates the presence of an amebic hepatitis. However, it should be realized that even in the absence of intestinal manifestations the condition should be considered, repeated stool examinations should be done, and every attempt made to confirm or exclude the diagnosis of amebic hepatitis. The significance of early recognition of this condition has been emphasized repeatedly and lies in the fact that the institution of appropriate therapy during this presuppurative stage may prevent progression to abscess formation.<sup>133, 277, 278, 285, 287, 329</sup> This is clearly demonstrated by Case I reported herein.

Whereas there is some variation in the clinical manifestations of amebic hepatic abscess depending upon the chronicity of the process, persistent hepatomegaly, pain and tenderness over the hepatic area with occasional radiation to the shoulder, and a daily remittent or intermittent fever of moderate degree are fairly constant manifestations. The presence of these symptoms and signs should always suggest the possibility of an amebic hepatic abscess. Anorexia, loss of weight and strength, nausea and vomiting, profuse perspiration, and disturbed slumber are less constantly observed, but their presence lends further support to the diagnosis. The presence of an antecedent dysentery is confirmatory evidence but its absence is not refutatory. It will be recalled that from one-third to almost one-half the patients gave no history of a previous dysentery. The diagnosis is supported further by a mild leucocytosis without a disproportionate increase in polymorphonuclear leucocytes. If, in addition to such a clinical picture, the characteristic fluoroscopic and roentgenologic findings previously described are present, the diagnosis of amebic hepatic abscess is justified. The demonstration of active or encysted forms of *E. histolytica* is corroborative evidence but their absence does not exclude the diagnosis.

It must be realized, of course, that whereas these findings justify the diagnosis of amebic hepatic abscess, its establishment depends upon the demonstration of the characteristic chocolate sauce pus (Fig. 1). Herein lies the diagnostic importance of exploratory aspiration. However, the procedure should not be performed without thorough cognizance of its possible dangers. Of these the most important are (1) hemorrhage, and (2) extension of infection. Various investigators have directed attention to the possibility of hemorrhage and have reported cases in which this dangerous complication followed exploratory aspiration of an amebic hepatic abscess.<sup>425</sup> Fatal hemorrhage occurred in over 20 of the reported cases according to Huard and Meyer-May;<sup>174</sup> Hatch<sup>160</sup> and Rogers<sup>326</sup> have emphasized the fact that this danger is greater in the acute stage of hepatitis with pronounced congestion of the liver. Accordingly, it may be almost entirely avoided by the administration of emetine for several days preceding the aspiration and thus controlling the associated hepatitis. As previously emphasized by us<sup>287</sup> extension of infection is another danger which deserves special consideration.

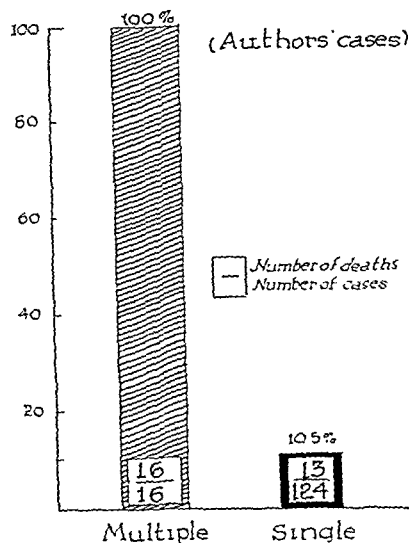
Since it is not always possible to determine clinically whether an amebic hepatic abscess is sterile or contains pyogenic organisms, the latter possibility should always be assumed and the aspiration performed in such a manner that an uninvolved portion of the peritoneum or the pleural cavity is not traversed by the aspirating needle. Obviously this is not always possible but the consideration should be kept in mind during the attempted aspiration. It should be realized, also, that this is not as difficult in the presence of an enlarged liver containing an abscess as under normal conditions, for in the former the anatomic relationships have been changed.

These hazardous possibilities, hemorrhage and extension of infection, may be avoided largely by preaspiration emetine therapy, the type of needle employed, the technique of aspiration, and the performance of the procedure in the operating room under absolutely aseptic precautions. Emetine hydrochloride should be administered for at least two to four days prior to aspiration in one grain (0.06 Gm.) doses daily. By employing a needle not longer than 10 cm. with a calibre not greater than 2 mm. the danger of puncturing a large vessel is minimized.<sup>174, 219, 233</sup> We prefer a short beveled needle or a trocar type with a short, fairly blunt point. The procedure should always be performed in the operating room, first, because aseptic precautions are likely to be greater and second, because if the abscess is found to be secondarily infected open drainage can be done immediately. This latter possibility can be readily determined by an immediate smear of the aspirated pus which will reveal upon microscopic examination the presence of large numbers of bacteria and leucocytes in those cases in which secondary infection is present. Whereas general anesthesia can be employed, local infiltration analgesia using 1 per cent procaine hydrochloride solution is preferable. Nicking the skin at the contemplated site of puncture with a bistoury will facilitate insertion of the needle.

The cutaneous site of puncture and the direction of the introduction of the needle depend largely upon the clinical and radiologic findings. Accordingly, in the presence of localizing signs and pointing of the abscess, the needle should be introduced directly over the mass or at the site of greatest tenderness. However, if no localizing signs are present, the roentgenograms may be of guiding significance. Thus, in a case in which the lateral roentgenogram demonstrates the abscess in the anterior portion of the liver, the needle may be inserted just below the anterior costal margin about 4 to 6 cm. lateral to the midline and directed superiorly and posteriorly (Fig. 22). On the other hand, if the lateral roentgenogram reveals posterior localization of the abscess, the needle should be introduced below the costophrenic angle and directed superiorly and anteriorly (Fig. 23). However, in those cases in which the abscess is located more anteriorly near the dome of the liver, as occurs most frequently, avoidance of the pleural and peritoneal cavities may be accomplished best by inserting the needle in the ninth or tenth

intercostal spaces in the anterior axillary line and directing it superiorly, medially, and slightly posteriorly (Fig. 24). Occasionally it may be necessary to puncture the liver in several different directions before pus is encountered. Accordingly, if multiple punctures are necessary it is extremely important to remove the needle entirely before reintroducing it in a different direction rather than changing its direction while the needle is still at its original site. In this way extensive injury to the friable liver parenchyma may be prevented.

*Prognosis:* A number of factors influence the prognosis in amebic hepatitis and hepatic abscess. In addition to the relative number and virulence of the parasite and the resistance of the host, the most important factors are: (1) the multiplicity of lesions in the liver; (2) the presence or absence of complications; (3) the presence or absence of secondary infection; and (4) the type of therapy employed.

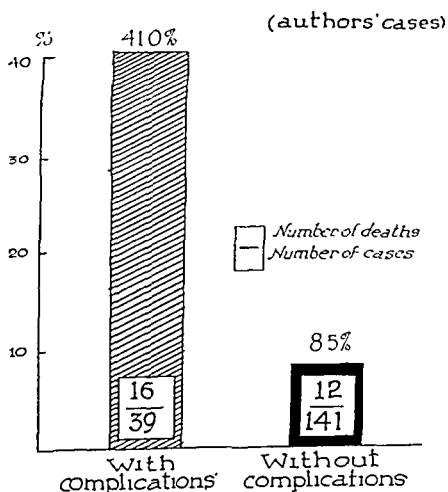


Graph X.—Mortality incidence of amebic hepatic abscess according to multiplicity of lesions in 140 cases of authors.

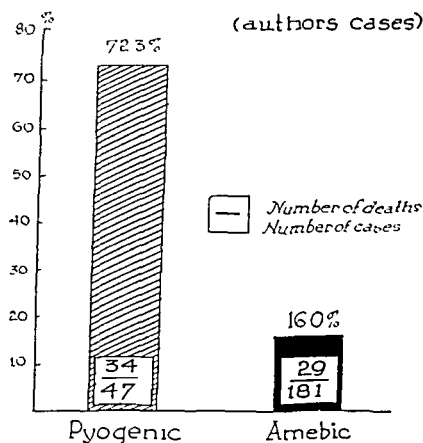
That multiple abscesses increase the gravity of the condition has been shown by a number of observers. Sambuc<sup>237</sup> found that the mortality was 23 per cent in cases with single abscess, 45 per cent in those having two abscesses, 90 per cent with three abscesses, and 100 per cent in patients having more than three abscesses. Of 137 cases with single abscess, analyzed by Huard and Meyer-May,<sup>174</sup> 23 (or 16.7 per cent) died, and in 13 cases with multiple abscesses the mortality was 100 per cent. Of 45 collected cases of multiple abscesses and recurrences Huard<sup>170</sup> found that the mortality was 44.4 per cent. Similar analyses in our series demonstrate further the prognostic significance of multiplicity of lesions. Thus, the mortality in 16 cases with multiple abscess was 100 per cent, whereas in 124 cases with single abscesses it was only 10.5 per

cent (Graph X). Of interest in this connection is the statement of Craig<sup>85</sup> that, "it is doubtful if the mortality of amebic abscess of the liver is ever less than 25 to 30 per cent if multiple abscess cases are included. . . ."

It is also to be expected that the presence of complications would influence materially the prognosis of amebic hepatic abscess. This is clearly demonstrated by the reports of various observers and the results obtained in our series. According to Huard and Meyer-May<sup>174</sup> the mortality in a series of 46 cases with complications was 34.7 per cent, whereas in a group of 104 cases without complications it was 19.2 per cent. This difference is even more pronounced in our series as the mortality in 39 cases with complications was 41 per cent in contrast with 141 cases without complications in which the mortality was 8.5 per cent (Graph XI).



Graph XI.



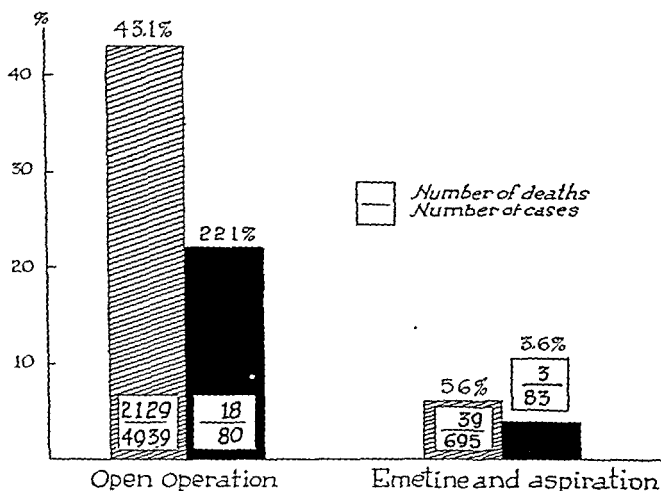
Graph XII.

Graph XI.—Mortality incidence of amebic hepatic abscess according to presence or absence of complications in 180 cases of authors.

Graph XII.—Respective mortality incidences in amebic and pyogenic hepatic abscesses based upon 228 cases of authors.

The fact, demonstrated above, that the majority of amebic hepatic abscesses are sterile is extremely significant in the prognostic as well as the therapeutic consideration of the condition. As emphasized previously, its decisive importance is insufficiently realized. After an amebic hepatic abscess becomes secondarily infected it can no longer be considered an amebic lesion but prognostically and therapeutically must be regarded as a pyogenic process. The invasive pathogenic and toxic characteristics of pyogenic microorganisms differ considerably from the relatively benign and limiting features of the purely amebic lesion of the liver. The contrasting mortality rates in the two conditions emphasize this fact with striking clarity. Thus, in a previously reported

series of 47 cases of pyogenic hepatic abscess the mortality was 72.3 per cent, whereas in this series of 181 cases of amebic hepatic abscess the mortality is 16 per cent (Graph XII). As previously stated, the deleterious effects of secondary infection of a sterile amebic abscess may be better realized if the analogy is made to the similar morbidiferous change which occurs in a tuberculous abscess that becomes secondarily infected.<sup>263, 326</sup> It is a well-established fact that the secondary infection of a tuberculous process greatly increases the gravity of the prognosis. For these reasons it is obvious that the avoidance of secondary infection in amebic hepatic abscess is paramount. Accordingly the type of therapy assumes increasing significance. In spite of meticulous care and scrupulous precautions to avoid it, secondary infection invariably follows open drainage of an abscess which is relatively sterile. Only by

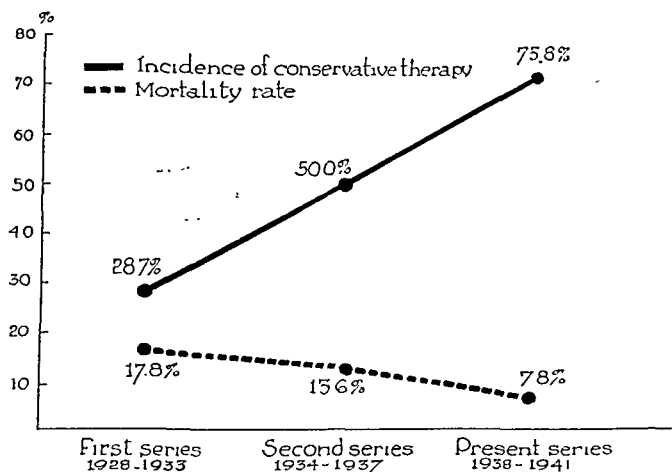


Graph XIII.—Mortality in amebic hepatic abscess according to type of therapy.

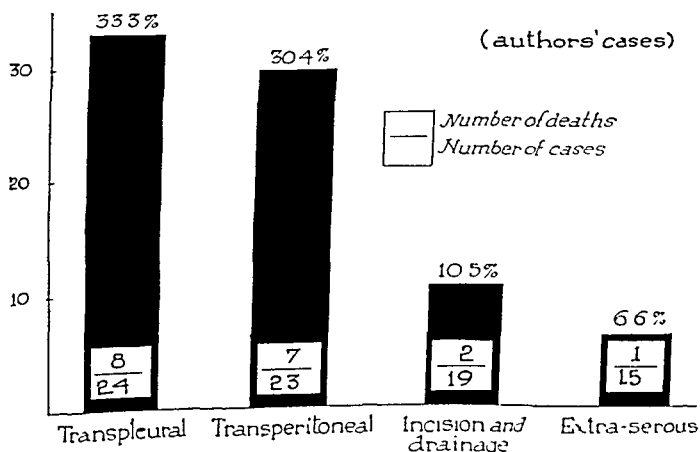
closed drainage, i.e., aspiration, is it possible to evacuate the abscess and simultaneously maintain its sterility. The striking contrast in the mortality rates obtained by various investigators who have employed the two methods of therapy irrefutably demonstrates this fact. Approximately 20 years ago, Rogers<sup>326</sup> made the observation that the mortality was decreased from 56.8 per cent in cases having open drainage to 14 per cent in those treated with closed drainage. Similarly, Chatterji<sup>50</sup> was able to reduce the mortality from 26 per cent in 69 cases with open drainage to 1.6 per cent in 186 cases with closed drainage. This is demonstrated more forcefully by the results in a large series of cases collected from various parts of the world. Thus, in a collected series of over 5000 cases the mortality was 43.1 per cent in those treated with open drainage,<sup>426</sup> and 5.6 per cent in those receiving closed drainage<sup>427</sup> (Graph XIII). These corresponding figures in our series were 22.1 per cent and 3.6 per cent (Graph XIII). Of even greater significance in



this connection is the consistent decrease in the total mortality rates in our cases during the three periods studied. This is undoubtedly due in great measure to the increasing employment of closed drainage. Thus, in the first series of 73 cases studied, the incidence of closed drainage was 28.7 per cent and the total mortality was 17.8 per cent; in the second



Graph XIV.—Respective mortality incidences in authors' three series of amebic hepatic abscess as compared to incidence of employing conservative therapy. Graph shows that mortality decreases as incidence of employing conservative therapy increases.



Graph XV.—Relative mortality incidence in amebic hepatic abscess according to type of operation in 81 cases of authors.

series of 66 cases these respective figures were 50 per cent and 13.6 per cent; and in the present series of 42 cases these corresponding incidences were 73.8 per cent and 7.8 per cent (Graph XIV). It may be graphically observed, therefore, that as the incidence of employing conservative therapy increases the mortality decreases (Graph XIV).

The prognosis of amebic hepatic abscess is also influenced by the type of operation employed in those cases in which open drainage is indicated. Since these cases are secondarily infected the contents of the abscess must be considered pyogenic. Accordingly, the institution of that type of drainage which completely avoids the slightest possibility of contamination of the two virgin serous cavities, the pleural and the peritoneal, becomes an absolute desideratum. As we have emphasized in previous communications,<sup>277, 281-287</sup> it is obvious that if an uninvolved serous cavity is in jeopardy of contamination by the type of drainage used the prognosis is much worse, not only regarding subsequent morbidity but also regarding life. The results obtained in our series of cases in which open drainage was used demonstrate these facts with graphic clarity. Thus, the mortality in 24 cases with transpleural drainage was 33.3 per cent and in 23 cases with transperitoneal 30.4 per cent, whereas in 15 cases drained by the extraserous route the mortality was only 6.6 per cent (Graph XV). There were 19 cases drained by simple incision over the abscess with a mortality of 10.5 per cent (Graph XV). Since these abscesses had become attached to the parietes and thus sealed off the serous cavities, drainage in these cases might also be considered extraserous. Accordingly, the total mortality in those having extraserous drainage would be 8.8 per cent contrasted with 31.9 per cent in those drained transserously.

*(To be concluded in the April issue. The references will accompany the last section.)*

# Book Reviews

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**Surgery of the Heart.** By E. S. J. King, M.D., F.R.C.S., Major, A. A. M. C., University of Melbourne. Ed. 1. Pp. 728, illustrations 268. Baltimore, 1941, Williams & Wilkins Company. \$13.50.

This monograph, fathered by a surgeon, is in many respects an unusual book. It essays to deal with surgical disorders of the heart from the standpoint of radiologic, clinical and electrocardiographic diagnosis, as well as surgical treatment. That obviously is an ambitious undertaking. Yet, the author has done this difficult task in a surprisingly effective manner.

The title of the book may suggest that the book was intended primarily for the surgeon. Such, however, is not the case, for the treatment of the subject matter from the technical, operative point of view is by no means exhaustive. It is not a book on operative surgery of the heart, though the essential features of operative procedures are described. The book is described best, probably, as a pathologic and clinical treatise on those diseases of the heart in which surgical treatment may play a useful role. A number of unusual conditions, such as tumors of the heart and cysts of the pericardium, are described. Yet the book fails to describe the surgery of patent ductus arteriosus or of peripheral arteriovenous communication which may provoke heart failure.

There is much to commend in the monograph. Those interested in the surgery of the heart will find the book an extremely useful source book.

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**Textbook of General Surgery.** By Warren H. Cole, M.D., F.A.C.S., professor and head of department of surgery, University of Illinois, and Robert Elman, M.D., Washington University, St. Louis. Ed. 3. Pp. 1067, illustrations 558. New York, 1941, D. Appleton-Century Company, Inc. \$8.

This general text on surgery has come to occupy an important place amongst textbooks of surgery. In this, the third edition, the authors invited well-known surgical authorities in their respective fields of interest to review the subject matter. Undoubtedly the authors got from these consulting collaborators a number of worthwhile suggestions which have pyramided the value of the text. The monograph embraces the entire province of surgery. The only surgical specialties which receive no notice in the book are those concerned with diseases of the eye, ear, nose, and throat.

The text is well illustrated and appropriate bibliographic references accompany each chapter. The authors, both teachers of surgery, obviously have lent a good deal of thought, time, and effort to compose a text which would be useful as a reference work for the general practitioner and, at the same time, meet the needs of the undergraduate student of surgery. Anyone who peruses the text carefully will agree that the authors have given American surgery one of its best general texts in the field.

# SURGERY

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## Original Communications

### THE PHYSIOLOGIC BASIS FOR THE SURGICAL TREATMENT OF ASTHMA

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FOR the purpose of this discussion asthma is defined as an abnormal type of respiration with labored breathing due to obstruction of the conducting airway system. Respiration is the total process of gas interchange, with breathing only one of its several related physiologic mechanisms. Respiration continually changes to meet the varying needs of normal life or to accommodate for the malfunction introduced by disease. Active inspiration and passive expiration suffice for normal quiet respiration and breathing is adjusted to greater normal demands by the chemical and reflex control of muscular activity. If the demand exceeds markedly the ability to ventilate, or the respiratory efficiency is embarrassed by either intrinsic or extrinsic pulmonary factors, labored breathing occurs. In asthma the factor is intrinsic widespread obstruction of the conducting airway system. Moreover, in some types of asthma this alteration in the normal function of the bronchial muscle and mucosa is initiated by excessive activity of reflexes which follow definite nerve pathways. When these reflexes originate in the lung, the afferent pathway traverses the sympathetic nervous system and may be interrupted surgically as the therapeutic measure.

#### THE RELATION OF STRUCTURE AND FUNCTION

The transition from terminal to respiratory bronchiole separates the proximal conducting from the distal exchange division of the lung. Their anatomic characteristics are distinctly related to function in abnormal as well as normal respiration. The epithelium gradually shifts from pseudostratified columnar in the trachea, and ciliated columnar in the terminal bronchiole, to nonnucleated respiratory plates in and

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beyond the alveolar ducts. Mucous glands, numerous in the trachea, are absent in the bronchioles. The bronchial muscle embraces the mucosa from the trachea to the alveolar mouths and despite an actual decrease, relatively increases by the fading out of other constituents. It is most prominent in the terminal bronchiole where the lumen is narrowest and unsupported by cartilage. Distally, as elastic tissue steadily replaces muscle, it changes to a myo-elastic layer. The tunica propria contains blood vessels, nerves, elastic fibers, wandering cells, and lymphocytes. The bronchial artery supplies the conducting, and the pulmonary artery the exchange division. The bronchial artery exhibits the typical innervation and reactions of the greater circulation of which it is a part.

The respiratory center integrates all respiratory functions. This formation of fibers and motor cells in the pons and upper medulla is especially fitted to correlate impulses from many areas. It has been divided into the pontile pneumotaxic, the inspiratory, and the expiratory (inhibito-inspiratory) centers. Impulses from the respiratory center adjust the vigor and rate of respiration by virtue of three characteristics; an automatic rhythm subject to modification by nervous and chemical factors; graded sensitivity to chemical stimuli; reciprocal innervation of inspiratory and expiratory centers. Automatic rhythm is established by chemical and nervous impulses inducing instability in one or several cells in the inspiratory nucleus. So-called "toppling" results in a burst of efferent impulses causing sustained inspiratory muscular contraction which Lumsden called apneusis.<sup>1</sup> Apneusis does not occur unless impulses which inhibit inspiration normally are excluded by vagotomy and pontile section.<sup>2</sup> These impulses follow two pathways. Those from the pulmonary stretch receptors, stimulated by expansion, pass in the vagi to the expiratory center and from there spread out to inhibit the inspiratory center. The original efferent discharge sends impulses to the pontile center which spread out to inhibit the inspiratory center and possibly excite active expiration. Thus, the center has no inherent rhythm but one dependent upon inhibition by either lung reflexes set up by expansion or reflexes from the pontile pneumotaxic center excited by the original inspiratory center discharge. Graded sensitivity of the respiratory center results either from the activity of a variable number of cells or from changes in synaptic resistance. This capacity may institute any activity from quiet respiration to dyspnea by quantitative control of muscular stimulation. Reciprocal innervation affects both phases of respiration. As impulses appear in inspiratory fibers they disappear in the expiratory and vice versa.<sup>3</sup> Pitts, Magoun, and Ranson<sup>4</sup> considered the expiratory center fundamentally inhibito-inspiratory after they noted that electrical stimulation in the medulla (of cats) usually inhibited inspiration but active expiration followed excessive stimulation only. Expiration becomes active when chemical or nervous stimuli are sufficiently intense and after the expiratory center is released from the inhibition of inspiration.

The respiratory center is affected by numerous chemical and nervous stimuli. It is so specifically sensitive to carbon dioxide that hyperpnea follows any slight increase in its concentration. Anoxemia, however, causes hyperpnea primarily through chemoreceptor reflexes rather than by central action. Although these reflexes do not regulate normal respiration since anoxemia is rarely severe enough, they may reflexly drive it in abnormal states when circumstances are sufficiently adverse to directly depress the center. Such hyperpnea may further impair the functional capacity of its neurons already depressed by local hypoxia. The consequent reduction of blood carbon dioxide lowers specific stimulation and contributes to cerebral vasoconstriction. Although carbon dioxide normally regulates respiration, intra- or extra-pulmonary reflexes are important since they may alter the respiratory pattern without evident blood chemical changes. While the Hering-Breuer reflexes and those reflexes from aortic and carotid zones are considered essential to the automatic control of respiration, others attain importance only in defective states like asthma. Definite anatomic pathways and physiologic effects have been demonstrated frequently for these respiratory reflexes. The sympathetic and parasympathetic divisions of the autonomic nervous system each contribute both afferent and efferent elements to the lungs where Ranson and Billingsley<sup>5</sup> found a wide variety of nerve structure.

Parasympathetic afferents run centrally in the vagus to the nodose ganglia, which most writers agree contain the cell of origin. Chase and Ranson<sup>6</sup> noted that these typically large sensory fibers disappeared from the vagus below the pulmonary rami. By vagotomy and degeneration, Larsell and Mason<sup>7</sup> showed that these came principally from the homolateral lung. Following the vagus rootlets and fasciculus solitarius they terminate in the nucleus of the tractus solitarius on cells which send fibers to the motor nuclei over the reticular formation. A reflex involving this pathway would traverse three neurons: a primary visceral afferent of the vagus; a secondary afferent with its cell in the nucleus of the tractus solitarius; a visceral efferent with a cell in the visceral efferent column.<sup>6</sup> Head's<sup>8</sup> study of the distribution of sensory spinal fibers through sympathetic pathways placed the lung supply from the upper five thoracic nerves. These originate in cells in the dorsal cerebrospinal ganglia,<sup>9, 10, 11</sup> not the sympathetic, and enter the sympathetic chain mainly in the upper three white rami.<sup>12</sup> Möllgaard<sup>13</sup> outlined their course over the vagus, ansa subclavia, stellate ganglia, and white rami to cells in the cerebrospinal ganglia of the upper three thoracic nerves. Their central processes pass to the dorsal horn and ascend or descend in the cord. Additional definite evidence indicates that many sympathetic afferent fibers reach the chain either directly or over the cardiac accelerator nerves.<sup>14, 15</sup> This pathway is easily traced and does not involve the cervical sympathetic trunk.<sup>11</sup> The lack of degeneration after vagotomy supports the sympathetic origin of these fibers which

traverse mainly the stellate, second and third thoracic ganglia, and white rami in reaching the cord.<sup>7</sup> Efferent parasympathetic fibers originate in the dorsal vagal nuclei and follow the vagus through the nodose ganglion to the lungs as preganglionic fibers. Larsell and Mason,<sup>7</sup> after vagotomy in rabbits, concluded that the majority of this motor supply was homolateral with minor cross-over in the posterior pulmonary plexus. Möllgaard<sup>13</sup> considered all of these efferent fibers either bronchomotor or secretory in function and further subdivided the bronchomotors into constrictors or dilators. This division is definitely open to question. The efferent sympathetic fibers from the intermediolateral cell column pass as preganglionic fibers via the white rami of the upper five thoracic nerves to the sympathetic chain. Möllgaard<sup>13</sup> believed that these fibers reached the vagus of the same and opposite side through the stellate ganglia and ansa subclavia and were vasomotor only. However, it has been proved that these fibers reach the lung directly or over the accelerator nerves and that they are not entirely vasomotor in function.<sup>15</sup> Rasmussen has supplied a diagram which graphically illustrates a conception of some of these pathways.<sup>16</sup> Larsell<sup>17</sup> has carefully described the sensory pulmonary terminations of these nerves and closely linked their location and structure to function. For example, at the division of the bronchi, bulbous nodules seem responsive to tactile irritation. In the respiratory bronchioles and alveolar ducts the thickened epithelial nodules seem fitted to react to the pressure stimulus of collapse. The most distal thinly encapsulated receptors in the alveolar walls and mouths are sensitive to distention. The sensory endings initiate all reflexes of pulmonary origin traveling the pathways already enumerated. The typical arrangement of preganglionic motor fibers to ganglia and postganglionic fibers terminating on smooth muscle cells, described by Ploeschko<sup>18</sup> for the trachea, applies to the bronchi also. Clusters of ganglion cells along the bronchi contain large nerve trunks having myelinated and unmyelinated fibers. Although most motor fibers are postganglionic, some leave the nerve trunks and go directly to muscle cells near the nuclei. It is not unlikely that these originate in cells at some distant source outside the lung. Since ganglion cells have not been found beyond the larger bronchi, the nerve bundles must carry sensory and both motor and inhibitory fibers. This anatomic variation closely parallels the marked difference in physiologic type of fibers found by Carlson and Luekhardt<sup>19</sup> in the pulmonary nerves of different animals.

Extensive experimental evidence indicates that impulses over these and other pathways markedly affect respiration. Those normal impulses which involve the pulmonary conducting system primarily are almost exclusively autonomic in course and reflex in type. Their hyperactivity is the basis of asthma. By section and stimulation of nerve endings, Dixon and Brodie<sup>14</sup> and Dixon and Ranson<sup>15</sup> outlined these reflexes which exert both a primary peripheral and a secondary central respira-

tory effect. They found with other factors constant that ventilation was measurably altered by any change in either the elasticity of the lungs or the resistance offered by the trachea, bronchi, or alveolar ducts. To stabilize elasticity, they eliminated variations in capillary blood, effusion, and secretion and studied the element of resistance. Muscular contraction appeared much more effective than mucosal edema and congestion in constricting the conducting lumen and increasing the resistance. By recording the changes in intratracheal pressure, airwave amplitude, and the phasic rate of respiration, they collected fundamental information on these reflexes which affect the lungs directly. Bronchoconstriction which decreases breathing, followed excitation of the distal ends of the cut vagus by stimulating motor constrictor fibers. These fibers, which originate in the dorsal vagal nucleus and supply the lungs over both vagi, are mainly homolateral in distribution but may cross completely. Similar constriction followed excitation of these endings by the parasympathomimetic drugs, muscarine and pilocarpine. Constriction is absent after nerve degeneration or atropinization. Vagal stimulation relieved constriction from pilocarpine by exciting a dilator reflex afferent in the vagus and efferent in the sympathetics.<sup>15</sup> Their conclusion that this vagal constricting action exerted no tonic effect on the bronchi may not be justified. These impulses induce a return of tonus during normal expiration and are significantly hyperactive in asthma.

Dixon and Ranson<sup>15</sup> studied the bronchodilator nerves in their re-investigation of the subject. Bronchial dilatation which increases breathing almost invariably followed stimulation of the peripheral ends of cut sympathetic fibers distal to the stellate ganglion. This contrasts sharply with the constriction from similar vagal stimulation. The motor dilating fibers, very few of which travel in the vagus, originate in the intermediolateral cell column and traverse predominantly the upper white rami to the sympathetics and stellate ganglia. Similar dilatation follows adrenalin excitation of the motor dilator endings or atropine paralysis of the motor constructor endings.

These efferent components have been linked to definite afferent arcs to complete the patterns of bronchial reflexes. Reflex bronchodilation followed stimulation of afferent fibers in the central ends of the sectioned vagi. This afferent impulse traverses the vagus to the medulla, descends in the lateral columns, and leaves the cord as an efferent impulse over the white rami of the upper three thoracic nerves. It reaches the lungs via the stellate ganglion but not entirely through the cervical sympathetic or cardiac nerves, since their section does not abolish it but high cervical cord section does. Stimulation of the central end of the cut accelerator nerves produces reflex constriction by impulses afferent in them and through the cervical sympathetics, stellate ganglia, and cord to the medulla. They excite, in motor nerve cells here, constrictor impulses efferent in the vagus. The vagus also contains a few afferent elements, the central stimulation of which causes bronchoconstriction.



These impulses are afferent and efferent in the vagus, section of which on the opposite side abolishes the reflex by interrupting the efferent limb. The profound significance of this mechanism is emphasized in the later discussion of sympathetic nerve block.

Numerous impulses which do not influence the respiratory cycle by any action on the pulmonary conducting system arise in widely separated areas. They are not exclusively autonomic in course but may follow such pathways. Their hyperactivity is a contributory factor in asthma. Head,<sup>20</sup> in 1889, recorded the contractions of the diaphragm as a means for investigating such afferent vagal impulses. Vagotomy induced a long contraction (inspiration) from increased tonus of the diaphragm. The chest assumed the inspiratory position with slower and deeper breathing which quickly returned to normal with the characteristic response to carbon dioxide. The increased tonus wore off or was lost after section of the efferent pathway in the phrenic nerves. Vagotomy temporarily increased the strength and duration of tonic and rhythmic inspiratory effort by obliterating the activity of normal vagal impulses which actually depress inspiratory effort. Similar reflex effects are conducted over extravagal paths. Gault and Scott<sup>21</sup> found that double vagotomy slowed respiration and prolonged inspiration, while low cervical cord section merely prolonged expiration. Combined, they lengthened both phases with slowing of respiration. Coombs<sup>22</sup> noted a decrease or cessation of costal respiration with a change in rhythm after dorsal root section. Coombs and Pike<sup>23</sup> observed that the slower respiration of double vagotomy was equally altered by section of either the dorsal roots or the corpora quadrigemina at the inferior colliculus. They, like others, concluded that the intercostal muscles excited afferent impulses which ascended over the dorsal roots and cord to the mesencephalon. However, it must be realized that dorsal root section also interrupts important afferent pathways from the lungs.

Head<sup>20</sup> clamped the trachea in different phases of breathing and re-studied the reflexes first described by Hering and Breuer in 1868. Lung distention inhibited diaphragmatic contraction (inspiration) with a pause normally occupied by relaxation (passive expiration). This pause was broken by a longer and stronger inspiration induced by the mounting carbon dioxide of asphyxia which overcame the nervous inhibition. Pulmonary collapse provoked a normally spaced inspiratory contraction. This was strong and prolonged since the clamped trachea prevented lung distention which normally inhibits inspiration reflexly. These reflexes changed quantitatively with extremes in either phase. The impulses from overdistention inhibited inspiratory contractions much longer than normal. This was not due to overventilation since the use of pure hydrogen did not alter it. Abnormal collapse produced by sucking air from the trachea caused immediate and vigorous inspiratory contractions. Head<sup>20</sup> visualized the vagus as the afferent pathway since its section obliterated these reflexes. Barry,<sup>24</sup> using similar methods, felt

that the inspiratory stimulus from the collapsed lung did not travel in the vagus. In the cat with the vagi and stellate ganglia excised, he found a definite decrease in the urge to inspiration. Moreover, it was completely abolished by cervical cord section but unaffected by vagotomy. He concluded that the impulse to inspire followed two routes to the cord. Those from the chest wall followed the somatic nerves, but those of pulmonary origin were transmitted over the sympathetics, stellate ganglia, and through the white rami to the upper three dorsal roots mainly. Both continued in the cord to the respiratory or other centers.

Larsell and Burget<sup>25</sup> elicited a forced type of expiration with polypnea by stimulating the tracheal and bronchial mucosa. The expiratory muscles were fully activated by a reflex which they believed was afferent in the vagus since its section abolished the response. Similar reflex activity involving both expiratory effort and bronchial constriction is commonly seen during bronchoscopy. Craigie,<sup>26</sup> with similar methods, obtained spasticity and irregular apnea from inspiratory inhibition. Finding vagotomy without effect, he concluded that these afferent impulses rose over the sympathetics and cord. Similar stimulation of the mucosa of the nose, pharynx, larynx, and trachea reflexly inhibited expiration over pathways in the trigeminal, glossopharyngeal, superior, and recurrent laryngeal nerves.

Normal respiration is the activity integrated by the normal impulses over these pathways. Impulses from the center efferent in the somatic nerves stimulate the inspiratory and inhibit the expiratory muscles. The tonus of the bronchial muscles likewise is inhibited during inspiration by efferent impulses over the sympathetics. It is restored during expiration by the uninhibited constricting impulses efferent in the vagus. This nervous control of bronchial tonus, which Macklin<sup>27</sup> considered reflex, changes the diameter and length of the bronchi and bronchioles. Thus, the capacity of the conducting system alternately increases with inspiration and decreases with expiration, and the major portion of the tidal air and vital capacity depends upon the maintenance of this flexibility. Relaxation permits adequate filling of the conducting portion. Tonic contraction diminishes ventilation of the next inspiration because it smoothly reduces this dead space without trapping alveolar air. Since the cross-section of successive branches of the conducting system is always larger than the parent stem, even with a decrease in individual size, and since the caliber of the exchange ducts steadily increases, the air current gradually slows. This slowing in the expanded conducting system aerates the alveoli and aids simple gas diffusion. However, the flexibility of the conducting system not only controls aeration, but also regulates the number of alveoli open for aeration. Since the capacity of the respiratory division depends primarily upon the number of alveoli aerated rather than upon expansion and contraction, adequate blood gas interchange, although a function of the respiratory division, depends

directly upon the conducting division. As the lungs distend, the sensory stretch receptors activate afferent vagal impulses which normally end inspiration by inhibiting it. Expiration occurs passively in this inhibited phase. In the hyperpnea of exercise the entire lung dilates temporarily, which, in the conducting system, increases midcapacity as the loss of bronchial excursion decreases vital capacity. In the respiratory portion the residual air increases because a maximum number of alveoli is maintained open. The retention of flexibility has, therefore, a direct effect on pulmonary efficiency.

#### ASTHMATIC RESPIRATION

In asthma gross malfunction occurs as abnormal impulses are initiated in the normal pathways. These abnormal impulses cause the replacement of normal bronchial flexibility by abnormal bronchial obstruction which in the conducting airway system is principally an expression of altered bronchial muscle function. Excessive stimulation of sensory endings in the bronchi excites afferent impulses which travel to the cord in the sympathetics either directly or via the stellate ganglia. After ascending in the cord to the region of the fasciculus solitarius, they stimulate in vagal fibers the efferent impulses of broncho-constriction. Irritation of other sensory areas may initiate similar reflex constriction. From the mucosa of the nose, pharynx, and larynx afferent impulses follow the olfactory bulb, glossopharyngeal, superior, or recurrent laryngeal nerves, but the efferent pathway remains in the vagus. The intensity of sensory irritation and the sensitivity of the receptors influence the degree of obstruction by controlling the number of the efferent constrictor discharges. Since these do not suffice to explain the relief observed after unilateral block or operation, it appears that some threshold of central afferent stimulation must be exceeded before constriction becomes evident clinically. With sufficient intensity abnormal spasm may result, and at the terminal bronchiole where constriction is normally greatest, it may partially or completely obstruct the airway. Incomplete relaxation reduces the ease and extent of inspiration. In expiration excessive tonus traps air distal to this point in the respiratory portion of the lungs, and the residual air rises. Thus in inspiration the toniccy of the bronchi with little flexibility reduces ventilation and diffusion, while in expiration by trapping of air and obstruction of alveoli it increases vitiation. If the bronchial tonus is severe, some alveoli may be completely shut off from gas exchange. The blood passing through these is not aerated and tends to reduce the effectiveness of aeration in other portions of the lungs. If the obstruction persists, factors other than the compromised conducting airway contribute to the alteration of the respiratory pattern. They are secondary to the obstruction to both phases of breathing and exert their action on the extrapulmonary respiratory apparatus. Inspiration becomes extremely active from central discharges which may be maximum. Their intensity,

though influenced largely by hypercapnia, may be affected by somatic reflexes not unlike those of exercise. This activity does not originate in the lungs since experimentally it follows only marked collapse. Inspiration is characteristically short because of prompt inhibition. The abnormal distention initiates over the vagus a continuous stream of afferent inhibitory impulses which are augmented by any further inspiratory effort. Head<sup>20</sup> showed that such prompt inhibition by extreme distention was followed by an abnormally long pause occupied by passive expiration. In asthma, however, expiration is active throughout this period since the air must be expelled through a markedly constricted conducting system. This excitation of expiration is a part of the preceding inhibition by impulses which have sufficient intensity to spread out as expiratory stimuli. If all these conditions progress, carbon dioxide and oxygen may reach levels in the blood at which carotid sinus or similar reflexes must supply the drive to respiration in the presence of failing central neurons.

Breathing assumes a different form if asthma has produced permanent structural changes in the lungs. Rupture of the septa in emphysema, the common end result of asthma, alters the pulmonary reflexes. Inspiration is almost continuously stimulated by impulses excited in the pressure receptors by the collapse of the septa. The inadequacy of stretch receptor stimulation in the collapsed septa and the slight expansion of the lungs inhibit inspiration poorly. Asthma becomes fixed, much as hypertension, when acute attacks aggravate the compromised respiratory system. Other predominantly vagal effects, similar to the reaction of bronchial muscle, may contribute to obstruction. Mucosal edema, vascular congestion, and excessive secretion commonly occur in clinical asthma, but changes in pulmonary circulation do not appear to be prominent primary factors.

#### THE CLINICAL TYPES OF ASTHMA

This concept of asthma is supported by the common division of this syndrome into clinical types. In one, definite allergic sensitivity is exhibited in various degrees. The acute rhinitis of early hay fever displays an increased sneeze reflex, but in more severe cases minimal wheezing or typical asthmatic breathing may occur. In the larger portion of this group, breathing is obstructed principally by mucosal edema, congestion, and increased secretion. It is worth noting here that sympathetic denervation by upper dorsal ganglionectomy produces similar changes in the nasal mucosa which persists for some time. During asthmatic attacks insufficient sympathetic activity likely produces comparable changes in the bronchi. Any spastic element of obstruction is a reflex from the upper respiratory tract or a direct effect on muscle. The common relief from atropine in early cases indicates that any direct spastic action on sensitized bronchial muscle is relatively unimportant.

The ability of these mucosal reactions to produce obstruction is clearly illustrated by the clinical features of angioneurotic edema.

The other large asthmatic group manifests no distinct allergy but is usually associated with recurrent infection in some portion of the respiratory tract. The irritation from this infection stimulates the receptors which initiate the reflexes of constriction afferent in the sympathetics and efferent in the vagus. The bronchus is not always the point of origin of this reflex. Sinusitis or other forms of upper respiratory infection which commonly recur in the presence of abnormalities frequently precipitate such reflexes. However, intrapulmonary infection usually initiates this reflex which is always efferent in the vagus. Any direct muscle sensitization must be minimal since skin tests are usually not markedly positive. In all these reflexes the sensory receptors are either sensitized or overstimulated, or the central threshold is lowered. Although the severity and persistence of attacks indicate that spasm is the most important factor, edema, congestion, and increased secretion certainly are present always.

Numerous pharmacologic studies demonstrate the essential hyperactivity of the autonomic nervous system in asthma. Atropine and scopolamine dilate bronchi and reduce secretion by paralysis of the motor parasympathetic endings. Dixon<sup>28</sup> found that pilocarpine and eserine constricted bronchi and increased secretion by stimulating these endings. Sollman and Gilbert<sup>29</sup> observed that the constriction from parasympathetic stimulants was blocked by atropine. Adrenalin dilates bronchi by stimulation of the motor sympathetic endings which inhibit constriction. Any effect upon the mucosal changes depends upon bronchial vasomotor action. Studies on bronchiolar response to anesthetic agents and related drugs yield similar data.<sup>30</sup> Ether, chloroform, and vinethene, which relax bronchi, have been shown to stimulate the sympathetics.<sup>31</sup> Ethylene and nitrous oxide have no significant effects. Cyclopropane produces constriction. In all instances the constrictor response was enhanced by eserine and prevented by atropinization. The frequent occurrence of lower respiratory tract obstruction during cyclopropane anesthesia in patients with asthma or hay fever indicates the hyperactivity of the motor parasympathetic system, which is readily reversed by intravenous atropine or by changing to a sympathetic dilating agent such as ether.<sup>32</sup> The barbiturates have a bronchoconstrictor action.<sup>33</sup>

#### THE PRINCIPLE OF THERAPY

The rationale of the surgical treatment of asthma rests upon these concepts. In that large group of so-called infective bronchial asthmatic subjects having few allergic manifestations and little benefit from desensitization, surgery has been most useful. Since the spastic factor in these cases involves a reflex originating in the bronchi, which is afferent over sympathetic and efferent over vagal paths, sympathectomy has been

advocated. The afferent path over the stellate and upper thoracic sympathetic ganglia has been interrupted by block or excision in a large number of patients, and the results form the basis of this report. The effectiveness of operation depends upon complete interruption of the afferent portion of the reflex of constriction. Although Leriche and Fontaine<sup>34</sup> and others<sup>35, 36</sup> have observed relief from stellectomy alone, the sensory pathways from one lung are more effectively eliminated by additional section of the upper thoracic sympathetic ganglia. Such wide resection abolishes at least one-half of those afferent impulses from the lungs, which in the presence of a lowered central threshold produce constriction. It does not disturb the normal afferent impulses in the vagus. Interruption of the dilator motor sympathetics by this procedure is evidently unimportant since their activity before operation has not inhibited attacks with maximal constriction. The failures of this method of treatment have been largely in patients whose long-continued asthma has caused emphysema. Three patients subjected to simple unilateral procaine block had immediate onset of status asthmaticus. Previously cited work indicates that this procedure removed a large part of the inhibition of reflex constriction which in these patients is both afferent and efferent in the vagus.

In the allergic group desensitization is the method of choice. It is not unlikely that mucosal changes and possibly direct action on muscle play major roles in the obstruction. If the constrictive element appears prominent but dependent upon a reflex of extrabronchial origin related to infection, the local condition should be corrected. This may indicate the removal of abnormalities such as polyps or treatment of sinusitis or other foci of irritation which initiate the reflexes. Although the afferent limb of these constrictor pathways varies, the efferent is always in the vagus. If this therapy does not obliterate obstruction, the posterior pulmonary plexus resection advocated by Rienhoff<sup>37</sup> may offer the only method of relief. However, this procedure disturbs reflexes which may be essential to normal respiration.

Each patient has been studied extensively before acceptance for surgical treatment. All patients had required frequent hospitalization for intractable asthma which had failed to respond to any and all treatment. Severe bronchospasm after diagnostic lipiodal installations demonstrated little more than extreme sensitivity of the bronchial system. Preoperative bronchoscopy revealed typically allergic mucosa. In every case bronchial irritation was considered the origin of reflex constriction. Through functional respiratory studies, the degree of pulmonary lability has been determined by observing the effects of bronchodilator drugs and nerve block on the vital and breathing capacities and residual air. The observed improvement is an acceptable index of the result that can be expected from interruption. Using these criteria, the following experience with nerve block and ganglionectomy is reported.

## NERVE BLOCK

Interruption of sympathetic pathways from the lung by nerve block has been found most useful as a diagnostic and prognostic procedure in the therapy of asthma. By no other method can one be certain that the reflex producing bronchospasm originates in the lungs and traverses the afferent pathway to be interrupted. If this origin cannot be conclusively established, no basis for neurolytic or surgical interruption of the upper dorsal sympathetic pathway exists. Asthmatic patients require special preparations for this procedure. Barbiturates are not used because of the bronchoconstrictor effect. Morphine which may raise dangerously the threshold for respiratory center stimulation is avoided. Scopolamine in doses which do not cloud the effect of block may be used. Thoracic sympathetic nerve blocks are completed with the patient in the sitting position to facilitate respiration. The posterior approach for stellate block and the standard technique of Labat for the thoracic ganglia is recommended. An effective nerve block in this region is indicated by the presence of a homolateral Horner's syndrome and temperature increase with anhidrosis in the affected area. Five cubic centimeters of  $1\frac{1}{2}$  per cent procaine solution in normal saline are injected at each ganglion. After ten minutes, if the block is effective with recession of symptoms, 3 c.c. of absolute alcohol are deposited. It should be emphasized that successful sympathetic block may precipitate status asthmaticus in a small minority of patients. Interruption of the motor sympathetic dilator pathways in these patients leaves the motor vagovagal pathway completely uninhibited. Alcohol injections are never to be completed under these circumstances. Therapeutic procedures such as endotracheal intubation to provide oxygen or intravenous atropine may be needed to sustain these patients for the duration of the procaine anesthesia. The stellate is blocked shortly before the thoracic ganglia, since the majority of sympathetic pulmonary pathways pass through it. A favorable block is often dramatic. The patient experiences the sensation of easier breathing and respirations tend to become more normal. Coughing and copious expectoration may follow after several minutes. Most patients complain of dizziness and become pale. Syncope, which is not uncommon, is attributed to dilatation of cerebral vessels. Such dilatation has been observed after experimental stellate block with procaine while the dura was open during intracranial operation.

Pneumothorax, which is a risk in any thoracic nerve block, is a potentially fatal hazard in the asthmatic patient because it is usually tension in type. For this reason nerve block in the status stage is not advocated. It should be completed during a milder period. If it is used in the emergency therapy of status, as has been done in a few cases, the risk of this practice must be recognized.

Ninety-five anesthetic or neurolytic injections of various types have been completed for seventy-two patients. Twenty-four bilateral stellate

blocks were completed for seventeen patients, fourteen of whom had satisfactory sympathetic paralysis. Twelve had definite improvement. Bilateral stellate block was discontinued after a death during the procedure was experienced. This might be explained by the observation of Cromer and Ivy<sup>38</sup> who have reported that bilateral stellectomy sensitized the respiratory center to the impulses rising in the vagus nerve and caused respiratory paralysis. Twenty-eight unilateral stellate blocks have been completed for twenty-five patients. The right was satisfactorily infiltrated for eighteen patients and the left for two. Sixteen of the twenty patients were improved. The right stellate, second and third thoracic sympathetic ganglia were blocked for eighteen patients. Fifteen were improved. The right stellate and second, third, and fourth thoracic ganglia have been blocked for four patients and for two others the fifth was included. Four of these 6 patients successfully blocked were improved. The present practice is to block the afferent sympathetic pathway at the stellate and second and third thoracic ganglia on the right side.

In the entire group of sixty-one patients whose afferent pulmonary sympathetics were successfully blocked, immediate improvement was noted in forty-seven (78 per cent). Although many of these patients could not be followed for an extended time, complete relief has been observed in some for a maximum of thirteen months while in others symptoms have returned in from two to four months. Since nerve block was not effective therapy for prolonged periods, ganglionectomy has been performed. Surgical resection of the stellate and upper thoracic pulmonary sympathetics was limited to patients who had definite benefit from block. One patient in whom stellate block precipitated an acute attack had some relief from procaine block of the vagus in the neck. Then posterior pulmonary plexus resection was completed on one side, but no estimate of the result can be made until the other side is subjected to operation.

#### OPERATIVE PROCEDURES

Ether given by the carbon dioxide absorption technique with an oral endotracheal airway in place has been utilized for anesthesia. Extra-pleural resection of the sympathetics has been attempted. An incision is made between the vertebral border of the scapula and the spine. The muscles are divided and short segments of the upper ribs removed subperiosteally. The ribs are cut as near the spine as possible and preferably removed with some of the transverse process, particularly of the second and third vertebrae. The parietal pleura is mobilized sufficiently to visualize the vertebral artery. The stellate ganglion can then be easily identified with the branches which pass around the artery to the inferior cervical ganglion. After these are clearly identified they are divided as high as possible. The chain is then excised, being careful not to injure the brachial plexus. The excision of the chain is completed



to below the third or fourth ganglion. The lung is then inflated and the wound closed in layers with a catheter in the extrapleural space to prevent trapping of air. It is extremely difficult not to rupture the pleura in mobilizing it. If ruptured, it should be opened widely to prevent tension pneumothorax which is rapidly fatal to these patients.

A persistent Horner's syndrome which developed in all patients did not unduly hinder them. It has gradually improved but never cleared completely. On the operated side the nasal mucous membrane becomes succulent with a marked increase in secretion, mild dilatation of the blood vessels, and considerable edematous swelling. Whether this is related in any way to the cessation of the symptoms of sinusitis, which some of these patients have noted, is not clear at this time. The reaction to adrenalin, either by injection or topical application, seems to be roughly the same on both sides. Skin temperature rises (10 to 12° F.) have been observed invariably on the operated side. This has persisted for more than eighteen months in some cases. All except two patients have had unilateral sympathectomy which is usually sufficient to obtain a good result.

Twenty-one patients have been subjected to operation. The immediate relief previously observed from nerve block was increased by surgical section since there is more effective interruption of the afferent pathways. All patients exhibited additional gradual improvement, probably from the delayed clearing of the lungs, aeration of more alveoli, and possibly adrenalin sensitization. They have been observed for a minimum of three months and a maximum of two years. All have had complete relief of asthma since operation. None have needed bronchodilator drugs despite the fact that most of the patients have not known where "to stick the next shot" since they were so sore from almost constant medication. This is not unexpected since only patients having good response to block have been submitted to operation.

A detailed report of the techniques for nerve block and surgery together with a complete account of the results obtained is in preparation.

#### SUMMARY

1. The breathing in some types of asthma is the response to exaggerated reflex activity in pathways that carry normal respiratory reflexes.

2. A review of the pertinent anatomic and physiologic evidence is cited to construct these reflex pathway patterns. The excursion in the respiratory-conducting airway system essential to normal breathing involves marked relaxation and constriction of the bronchial muscles which may not be reflex in type.

3. Impulses, reflex in type, that produce both constriction and dilatation of the bronchi have been clearly demonstrated in these pathways.

The reflex of constriction is afferent with the sympathetic division of the autonomic nervous system and efferent in the vagus nerve. The reflex of dilatation is afferent in the vagus and efferent in the sympathetics. It is inhibitory in type.

4. The reflex afferent impulses of constriction travel predominantly over fibers in sympathetic pathways which may be interrupted at the stellate and second, third, and fourth thoracic ganglia.

5. Bronchial asthma precipitated by recurrent infection in the bronchi is dependent, not unlikely, upon excitation of this reflex of constriction. It can be benefited by interrupting this reflex before damage to the lungs has become irreversible.

6. Blocking the pathway of this reflex is the most reliable method for determining its pulmonary origin. If such origin is not demonstrated, no indication for interruption of the pathway exists. Furthermore, nerve blocking is useful to differentiate the types of asthma.

7. The application of neither anesthetic nor neurolytic solutions has resulted in permanent interruption of these pathways. The results from surgical excision have been more complete and permanent.

8. The experience of this study demonstrates that surgery is an important merited therapeutic procedure if it is restricted to patients with asthma of pulmonary origin who have been carefully selected after benefit from nerve blocking.

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## FASCIA LATA TRANSPLANT FOR DIFFICULT HERNIAS

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WE ARE all cognizant of the fact that in the evolution of the surgical art—as of other arts, plastic or graphic—there were epochal discoveries and innovations which served as symbolic milestones. This is particularly true of the progress of hernial surgery, but with the important reservation that the aforesaid milestones were few indeed on the horizon-less road of history. For over 800 years there was a Dark Age in hernial surgery. Primitive concepts held sway to within comparatively recent years concerning the etiology of this world-wide affliction, concepts, and practices which to us moderns, would seem to transcend the limits of human credulity but which received the sanction of “surgical” custom.

I do not refer merely to the ancient surgical customs, for be it remembered that it was not until Joseph Pancoast's day—in the 1860's—that any one in the United States attempted to operate on reducible inguinal hernia, such was the great dread and near certainty of a fatal issue.

Bassini of Padua described novel operations for inguinal and femoral hernia which proved revolutionary. They were, in effect, the first rational advances in the surgical repair of hernia in over 2,000 years, since Babylonian and ancient Egyptian days. Bassini's operation was based on a sound anatomic basis and therefore received world-wide acceptance.

W. S. Halsted almost concurrently with Bassini devised a new operation for inguinal hernia which in some regards closely resembled that of Bassini, in which an attempt was made to re-establish the obliquity of the canal. The spermatic cord was placed on the internal oblique muscle. Halsted constructed a new canal and ring but transplanted the spermatic cord superficial to the aponeurosis of the external oblique muscle.

A number of other innovators in surgery advocated the use of various flaps of fascia, periosteum or bone in one way or another to overcome the admittedly unsatisfactory results in hernial surgery. Kirschner, with this objective in view, in 1910, first suggested the feasibility (and later recanted somewhat) of repairing various anatomic defects with a sheet or strips of fascia lata. In the same year Mackenzie utilized the iliotibial band of the tensor fasciae latae in the repair of large abdominal wall defects.

McArthur, in 1901, was the first to employ living fascia as suture material. He utilized a narrow pedicled strip from the aponeurosis of either flap of the split external oblique and sutured the structures to the aponeurosis with these strips.

Gallie and LeMesurier's great contributions to hernial surgery are, of course, well known. They demonstrated, with clinical and experimental evidence derived from rabbits and dogs, that long strips of fascia lata were ideal suture material for the repair of otherwise inoperable or recurrent hernias (Figs. 1 and 2).

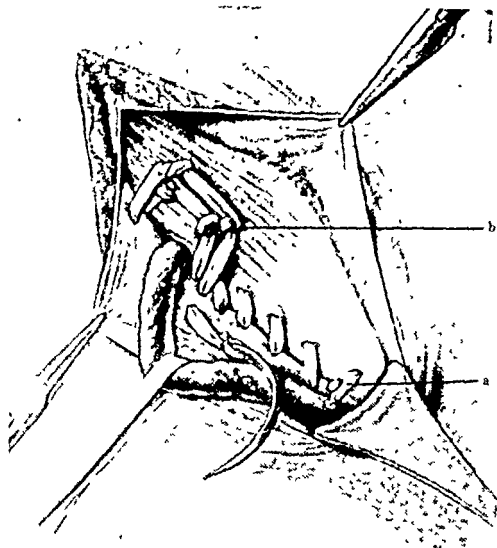


Fig. 1.—Repair of inguinal hernia with sutures of fascia lata. Insertion of first row of sutures. (a) Shipknot anchoring stitch. (b) Lock stitch. (Courtesy of Dr. W. E. Gallie.)

Gallie and LeMesurier's results found considerable confirmation in the later researches of Gratz<sup>1</sup> concerning the tensile strength and elasticity of human fascia lata. This investigator found that, "The material showed surprisingly great tensile strength, comparing favorably with soft steel wire of the same weight; in addition, it showed an unexpected degree of elasticity."

While many surgeons today (Seelig and Chouke<sup>2</sup>) have serious doubts concerning the value of ordinary sutures in fixing the conjoined muscles and the inguinal ligament they are not, on the other hand, in agreement with the Gallie and LeMesurier contention that no post-operative evidence is found of previous fixation with the usual technique. It is contended that the Canadian surgeons failed in their dissections to identify properly the atrophic, frayed-out muscles—often all that remains following fixation. Muscle, deprived of function, rapidly atrophies; this change is hastened by the constant pressure to which it is subjected. This holds particularly true, it is maintained,

when the transversalis fascia is defective and there is a concentration of intra-abdominal pressure perpendicular to its fibers. Careful observation will demonstrate, at the least, the margin of the muscle still adherent to the ligaments, though the fibers may be so separated and frayed that recurrence is not surprising.

Seelig and Chouke<sup>2</sup> undertook to investigate the moot question of the union of muscle and fascia. They concluded that "normal muscle will not unite firmly with fascia and ligament. It is, therefore, a useless procedure to suture the abdominal muscles to the inguinal ligament in the hope of buttressing a weak or ruptured abdominal wall."

A. R. Koontz,<sup>3</sup> on the other hand, demonstrated clearly that muscle united with fascia, owing to the union of the latter with the fibrous components of the former.

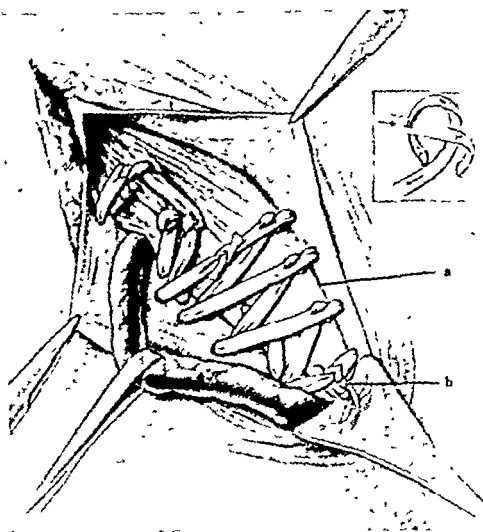


Fig 2.—Repair of inguinal hernia. Insertion of second series of sutures between external aponeurosis and inguinal ligament. (a) Junction line of aponeuroses of internal and external oblique muscles. (b) Termination of suture. Insert: practical lock stitch. (Courtesy of Dr. W. E. Gallie.)

Many surgeons object to the use of autogenous fascial sutures in hernial surgery. It is argued that infections are more common than with the older methods and that the introduction of large needles through the transversalis fascia and the inguinal ligament frequently leaves weak spots which predispose to recurrences. Burdick and associates<sup>4</sup> came to the conclusion, after 1,485 hernia operations, that the theory of fascial sutures for repair is based on an erroneous surgical principle!

Some surgeons, further dissenting, state that the use of the iliotibial tract of the tensor fasciae femoris muscle is unsound in surgical principle and wholly devoid of the merits commonly ascribed to the technique for the procurement of transplants therefrom. The rejoinder,

nevertheless, from the proponents of the ingenious surgical procedure, is that it is justified on the following theoretic and practical grounds.

1. It is, above all, an attempt to produce better results.

2. Closure of large defects in the floor of the inguinal canal is not invariably successful.

3. Strips of fascia are nonabsorbable and do not tear through after insertion.

4. It is evident that living fascial sutures, unlike other sutures, do not drag the inguinal ligament and the tendo conjunctus together, distorting their relationships. The integrity of the inguinal ligament is preserved with their use. The darning serves as a re-enforcement in Hesselbach's triangle.

5. The iliotibial band is the only accessible and mobilizable fascial musculature available, retaining its myodynamic integrity, that is, elasticity, contractility, and extensibility. The viability and therefore the tensile strength of a graft depends, first, on its connection with a base and the preservation of its nerve and vascular supply and second, on the width of the link. The nerve and vascular supply, highly situated, are not disturbed or destroyed.

6. The requisite amount of fascia is procurable from both thighs, if necessary.

7. There is no loss of bodily function in the transference of the graft.

8. The contiguous biceps femoris and vastus lateralis muscles do not herniate much, if at all, because they have their own fascial enveloping sheaths.

9. Surgical experience sustains the validity of the foregoing statements. The transplantation of a live structure with intact nerve and blood supply is fully effective because the tonus of this musculofascial structure is preserved. An abdominal wall defect becomes such post-operatively by virtue of the fact that the tissues utilized to close it have no tonus. The collagen fibrils which constitute fascia possess the sole function of constant tension in an elastic manner; the requisite tonus is thus maintained. An examination of the groin in a patient for whom a fascial transplant has been utilized reveals the firmness, and it may be added, the contractility and tonicity, of the band. In brief, instead of closing a physiologic anatomic defect with a lifeless structure, a viable physiologic and anatomic one is used.

The strongest union takes place when white fibrous tissues are approximated without tension. When two living fascial planes are approximated there is complete and enduring union.

It is manifest, therefore, that the use of living fascia in the repair of large hernias is of transcendent value as compared to all other forms of suture material.

The common experience of surgeons has been that grafts of animal tissues, unless they are autogenous, are unsuccessful, being fated to absorption and other changes.

Heterogenous fascial sutures, it is stated, function by stimulating tissue repair, but I have not observed any advantage in their use. Contrariwise, these foreign structures often undergo necrosis and degeneration. The employment of heterogenous fascial sutures, it seems to me, should be discouraged.

Anatomists and surgeons have for a long time been aware of the fact that fascial and aponeurotic structures are the main supporting and enveloping tissues of the body. Surgeons utilized fasciae, aponeuroses and their derivatives, to obliterate defects (congenital, acquired postoperative, and traumatic) in the abdominal wall and inguinal regions. An approach to perfection in the use of aponeuroses and fasciae has not perhaps been thought possible because of our failure to take advantage of what one may call the "natural resources" of the human body.

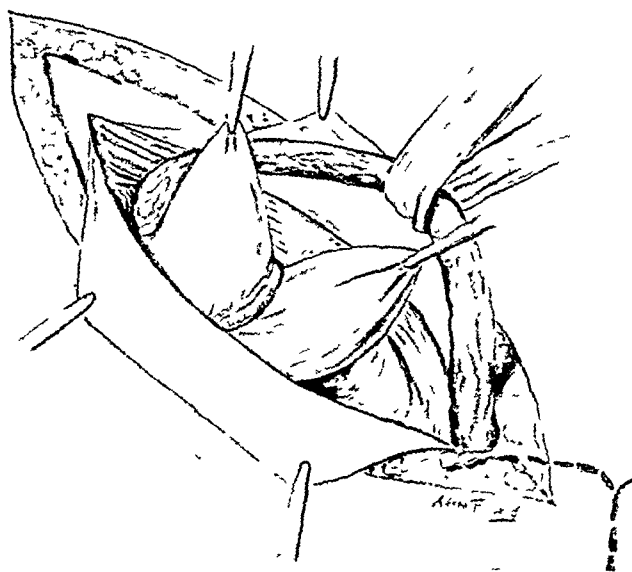


Fig 3—Pantaloons or saddlebag hernia, inferior epigastric vessels forming a bilocular sac. Condition found in Case 2.

Architecturally, the inguinal canal may be considered a funnel-shaped structure. From a purely mechanical viewpoint it is, therefore, sound surgery to obturate the inlet to this tunnel rather than the outlet in order to prevent effectively the intrusion of an abdominal viscus, part thereof, or of an associated structure.

One does not marvel at the nearly universal, excellent results obtained by the orthopedists in tendon transplants, to wit, the utilization of the peroneus longus in paralysis of the tibialis anterior muscle, and the role played by the teres major muscle in its transplantation in



Erb's birth palsy. The success of the procedure is undoubtedly dependent on the fact that living structures are used.

The paramount advantages of the utilization of fascia lata transplants, stated succinctly, are as follows.

1. Fascia lata transplant has a definite role in the repair of abdominal wall defects.

2. In direct and pantaloon hernias, with the high incidence of recurrence, it rarely fails (Figs. 3 and 4).

3. In hernias of the older group, of men and women past 50 years of age, it promises cures.

4. In the repair of "sliding hernias" (a problem in the past) a solution is at hand.

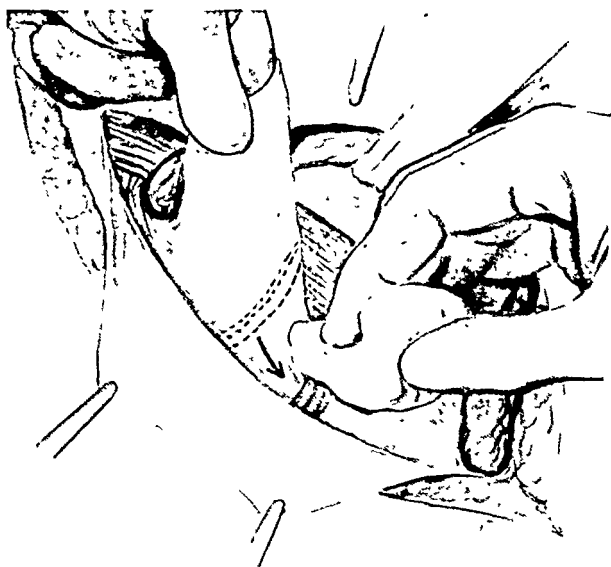


Fig. 4.—Pantaloon hernia converted into an indirect inguinal hernia by making traction on indirect portion and dislocating inferior epigastric vessels medially.

5. Despite wound infection, the results are excellent.

6. No disturbances of locomotion ensue.

7. Recurrences are rare.

Stated briefly, the indications for the utilization of fascia lata transplants are:

1. Hernias difficult to repair by the customary surgical methods.

2. Large or massive inguinal hernias, complete or incomplete, direct or indirect, with a structural defect in Hesselbach's triangle, and musculature and aponeuroses which have lost their myodynamic integrity.

3. Recurrent hernias with large defects in Hesselbach's triangle (Fig. 5).

4. Large or massive incisional hernias (Fig. 6).

The quintessence of the matter lies in the following: When extreme relaxation of the inguinal canal floor is present with loss of support in the inguinal triangle consequent upon the inadequacy of the transversalis fascia from one cause or another, whether it be weakness or absence, with loss of valvular function of the rings and loss of the physiologico-anatomic functions of the abdominal wall bulwark, the utilization of fascia lata transplants in a deep reconstructive repair has unparalleled values.



Fig. 5A (Case 5) —Right recurrent inguinal incisional hernia, and left saddlebag hernia.



Fig. 5B (Case 5) —After pedicle fascia lata transplant for right recurrent inguinal incisional hernia.

Fascia lata transplants, or any other variety of transplants, should not be used indiscriminately, whether in the groin or elsewhere in the body. Where the fascia transversalis has not lost its prime function, it is, in my opinion, an unsound surgical procedure. As in all ameliorative efforts, medical or surgical, patients should be strictly individualized.

In 1934, Wangenstein<sup>7</sup> described his method of repairing inguinal hernia by means of a pedicled graft from the iliotibial tract. The flap

is swung into the wound over the inguinal ligament and sutured over the spermatic cord.

Certain modifications of surgical technique were found advisable (Fig. 7).



Fig. 6 (Case 6).—Woman, aged 40 years, with large postoperative incisional hernia.

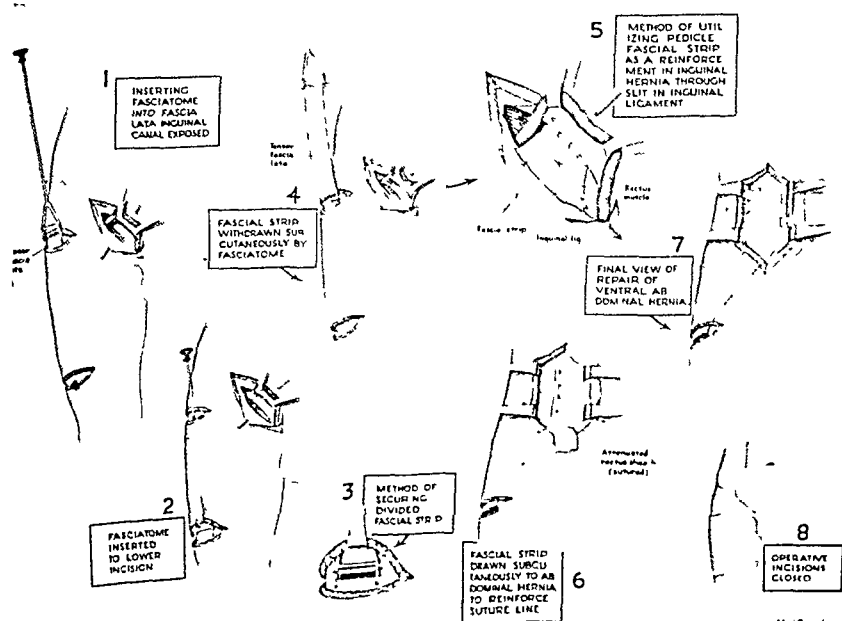


Fig. 7.—Pedicle fascial lata transplant in inguinal and ventral hernias.

I utilize the following technique for fascial sutures, a plastic operation for difficult inguinal hernias. The usual inguinal incision is made and the external oblique aponeurosis is split parallel to the inguinal canal. Extreme care must be taken to identify the external iliac,

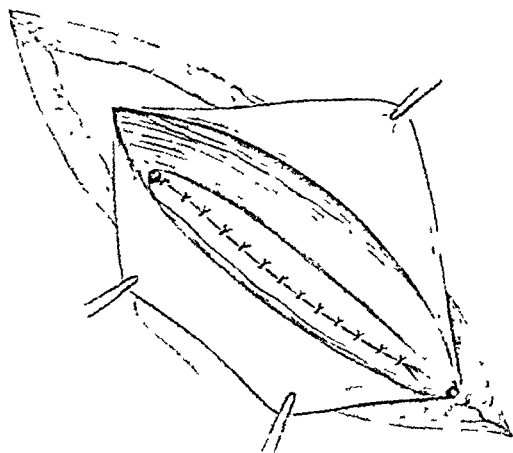


Fig. 8.—Redundancy of transversalis fascia in Hesselbach's triangle eliminated by interrupted plicating sutures.

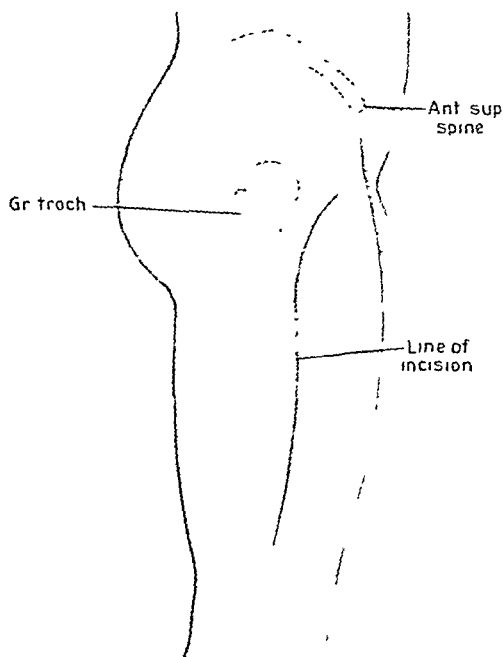


Fig. 9.—Skin incision for fascia lata transplant.

is swung into the wound over the inguinal ligament and sutured over the spermatic cord.

Certain modifications of surgical technique were found advisable (Fig. 7).



Fig. 6 (Case 6).—Woman, aged 40 years, with large postoperative incisional hernia.

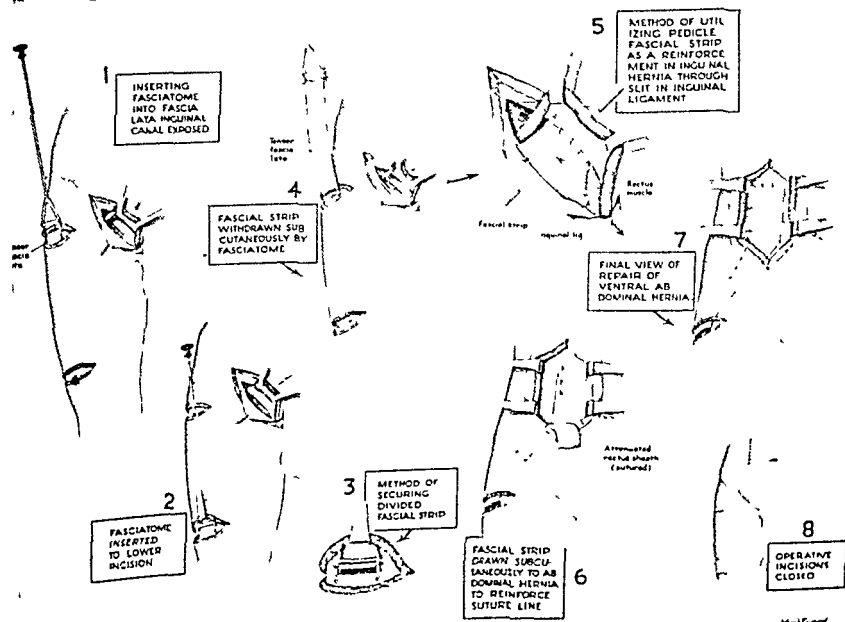


Fig. 7.—Pedicle fascia lata transplant in inguinal and ventral hernias.

plant and the center of the inguinal ligament (close to the slit) to the middle of the transplant. Three sutures are inserted, one at each angle of the gash and one in the center of the inguinal ligament. The free end of the transplant is then sutured to the tendo conjunctus and to the inferior aspect of the external oblique aponeurosis by No. 1 interrupted chromic catgut strands placed at intervals of about three-quarters of an inch. Care must be observed that the medial angle of the free edge of the pedicle is sutured sufficiently far medially so that it impinges upon the rectus abdominis muscle; the lateral edge of the free border of the fascial transplant must be sutured far enough to impinge upon the deep inguinal ring. The medial border of the fascial transplant above the inguinal ligament is then sutured to the superior aspect of the lacunar ligament to prevent herniation. A single suture is then placed, approximating the middle section of the transplant above the inguinal ligament to the underlying transversalis fascia in

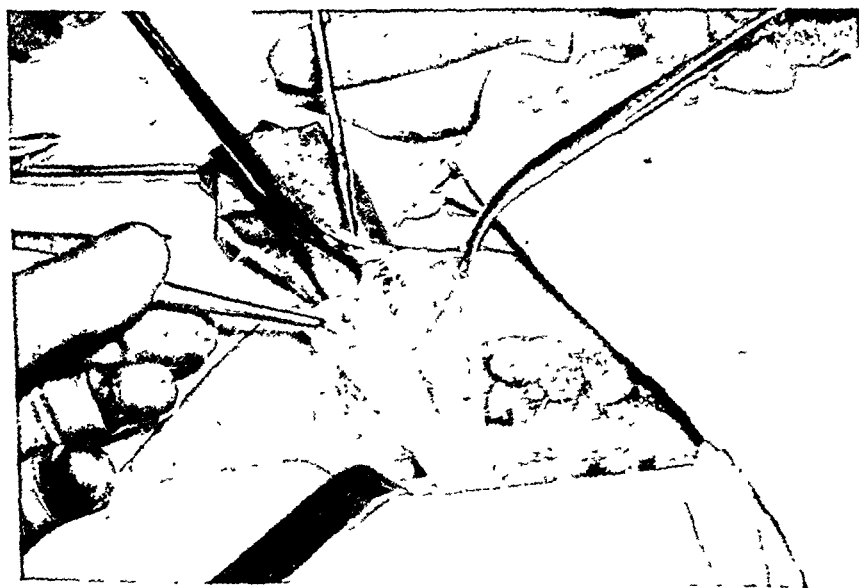


FIG. 11.—Pedicle flap of tensor fascia lata brought up as a re-enforcement subcutaneously.

order to eliminate dead space. The lower free border of the external oblique aponeurosis is finally sutured to the upper free margin (in the manner of the Wyllys Andrews repair) thereby placing the spermatic cord subcutaneously. Thorough hemostasis, as in all plastic surgical procedures, must be carried out. The skin is closed with black silk sutures.

In fashioning the fascial flap it is absolutely essential to obtain one sufficiently long to obviate tension on the suture line. Care must be

femoral and inferior epigastric vessels, in inguinal hernia. The external oblique aponeurosis is then divided parallel to the inguinal canal to a point just beyond the abdominal inguinal ring, being careful to avoid injury to the subjacent ilio-inguinal nerve. When there is a marked redundancy of the transversalis fascia in Hesselbach's triangle, it is taken up by a series of interrupted sutures inserted similar to vertical Lembert sutures (Fig. 8). A vertical incision is then made along the anterolateral aspect of the thigh, its upper end curved somewhat anteriorly from a point above the anterior superior angle of the great trochanter, downward as far as required, revealing the iliotibial band (Fig. 9). A sufficient section of this band is taken and of requisite width to reach, without tension, the entire hernial defect (Figs. 10 and 11).

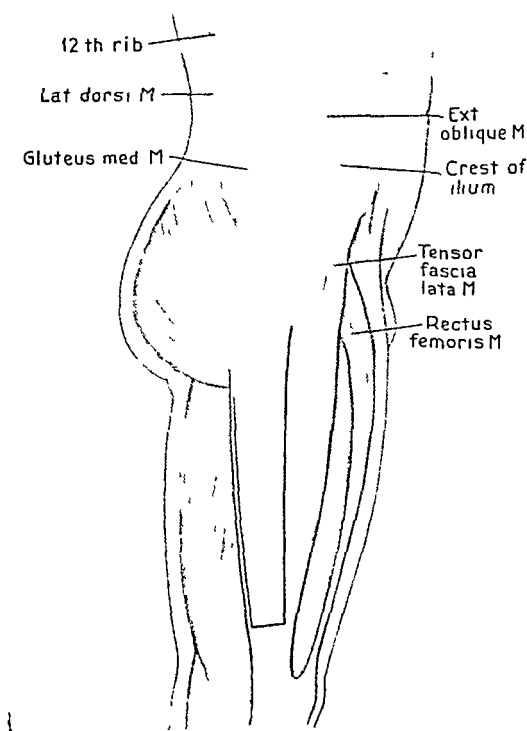


FIG. 10.—Delineation of the strip of tensor fasciae latae for fascial transplant.

A strip of fascia, three inches wide and two to four inches long, is usually sufficient, so that any tendency to herniation of the vastus lateralis muscle is averted. The pedicled fascial strip is then carried to the inguinal ligament subcutaneously. A slit is made in the inguinal ligament through which the fascial transplant is drawn. Three sutures are placed at this point in the ligament uniting the medial and lateral boundaries of the slit to the nearest portion of the fascial trans-

There were only four recurrences in my series of eighty cases with the use of fascia lata transplants. A bilateral fascia lata transplantation was done in one patient with a subsequent recurrence on one side, and in two I failed to suture the medial part of the transplant to the lacunar ligament, thus permitting a bulge to occur in that area. In the fourth case, a postoperative incisional hernia, a defect recurred at the upper angle of the wound.

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taken not to injure the external iliac or femoral vessels in splitting the inguinal ligament. The lateral margin of the flap, in the inguinal region, should be close enough to impinge upon the deep inguinal ring and yet not too far so as to constrict the spermatic cord and its constituents. The medial border of the flap, in the inguinal region, must be firmly secured at its lower margin to the lacunar ligament.

Slight variations in technique are followed (depending upon expediency) in repairing abdominal wall defects with these grafts. As Wangensteen aptly stated, "In the repair of incisional hernias, the flap is best sutured as a patch over the site of the closure, it being anchored securely to the normal adjacent fascial structures."

The fascia lata through the medium of the tensor fasciae femoris muscles has the crest of the ilium as an anchorage. The external oblique aponeurosis to which it is sutured has the lower seven ribs as an anchorage through the medium of the external oblique musculature. Thus, we have two firm structures alive with myodynamic attributes of contractility and mobility pulling against each other in a synergistic manner. Therefore, the best physiologic cure for an abdominal defect is utilized.

Recently I devised a fascial stripper, a fasciatome, enabling one to obtain pedicled fascia flaps of various widths subcutaneously through a small incision in the upper part of the thigh and one just above the knee. Thus the long scar, an objectionable feature of the procedure just described, is eliminated. A subsequent report will demonstrate the use of this instrument.

TABLE I  
EIGHTY CASES OF FASCIA LATA TRANSPLANTS

<i>Sex:</i>	
Males	75 cases
Females	5 cases
<i>Age:</i>	
Youngest	25 M
Oldest (sliding hernia)	67 M
Average	48 plus
<i>Types:</i>	
Indirect inguinal	3 cases
Direct inguinal	10 cases
Saddlebag or pantaloons	30 cases
Bilateral saddlebag	1 case
Sliding	11 cases
Incisional inguinal	19 cases
Incisional abdominal	6 cases
Total	80
<i>Recurrences:</i>	
Incisional inguinal	3 cases
Incisional abdominal	1 case
Total	4

ing tendency of fascia must be extraordinarily great to explain his large series of successes. He recognized the resistant quality of transplanted fascia even under the unfavorable circumstances of bad nutritional and septic conditions. Ordinarily, the graft would be subject to the cementing action of ingrowing connective tissue on both surfaces, but even when healing could occur on only one surface, such as when the graft faced the free peritoneal cavity, the result was successful. Furthermore, a transplant poorly nourished on both sides, such as one replacing the layers of the abdominal wall including peritoneum, and not covered by skin so that it was visible at every dressing, also remained viable. Dural defects could be grafted successfully even though one side is covered by bone and the other exposed to protein-poor cerebrospinal fluid. He cited one case, out of many, of fascial replacement of an abdominal defect secondary to a huge appendiceal abscess; this too was successful despite the presence of infection. Transplants under such conditions are not recommended, but such cases illustrate the extraordinary healing tendency of fascia.

#### FATE OF THE TRANSPLANT

Considerable controversy as to the histologic fate of transplanted fascia still exists. Kirschner observed grafts for 101 days and found that they retained their characteristic structure and healed practically unchanged. Experiments by Dean Lewis and Davis strongly supported this observation. Other observers found some evidences of degeneration, vascularization, and replacement, but Kirschner felt that the question of complete viability as such was, after all, purely academic since partial replacement by scar tissue made the transplant no less serviceable than normal fascia.

Neuhof, in a critical review of Kirschner's work, felt that he did not establish the viability of transplanted fascia by his experiments, but that he did place the method on a sound working basis. A summary of the prevailing thought on the subject is supplied by Neuhof: Fascia is a simple tissue, relatively poor in cells and blood vessels and is one of the most readily transplantable of all tissues, healing with minimal reaction, even under unfavorable circumstances. The early phenomena occurring about an autograft of fascia are agreed upon by all investigators. The transplant is promptly covered by a layer of fibrin, rich in leucocytes, that gradually undergoes organization, so that in two weeks a thick zone of cellular granulation tissue is found to surround the graft. The staining quality of the fascial cells as well as the intercellular substance suffers almost from the outset, indicating some degree of degeneration. Apparent recession of the degenerative phenomena is seen in the succeeding weeks. Is this really the case or are we dealing with the early evidences of gradual replacement? Mimicry of the appearance of any original graft by the replacing tissue occurs frequently. The question of the persistence or replacement of fascial transplants has been

## FREE AUTOPLASTIC TRANSPLANTS OF FASCIA LATA IN THE REPAIR OF LARGE INCISIONAL HERNIA

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### HISTORIC REVIEW

THE anatomic closure of hernial defects described by Bassini and Halsted marked the advent of modern hernial surgery. The failure of these methods in the treatment of many large and difficult hernias had early stimulated surgeons to search for suitable strengthening materials. All methods using nonabsorbable foreign materials, such as celluloid plates, silver screens, paraffin, metal staples, etc., have been abandoned. The almost unanimous experience of surgeons has been that grafts of animal tissues, unless they are autogenous, are unsuccessful, being fated to absorption, to calcification, to mere toleration as of a foreign body, to sloughing, or to replacement with connective tissue.

The major advance in the surgical treatment of hernia has been the utilization of fascia. Wölfler, in 1892, and later Halsted turned down a flap of anterior rectus sheath and sutured it to Poupart's ligament. In 1901, McArthur used as a fascial suture a strip cut from, but left attached to, the adjacent edge of the incised external oblique aponeurosis. Then followed the development of three plastic procedures which are more or less in popular use today. Kirschner first demonstrated, in 1909, the successful use of free autoplasmic fascia lata transplants. In 1921, Gallie used "living sutures" of fascia lata strips to fill hernial defects by weaving them into a latticework. Wangenstein, in 1933, employed the iliotibial tract of fascia lata as a pedicled flap in the repair of recurrent and difficult hernias and other large defects of the abdominal wall. The use of free fascial grafts has enjoyed frequent reports in the German literature but has received scant attention by American writers. We believe that this method has not received the acclaim that it deserves and that a review of its background will establish a convincing basis for its use.

Clinical and experimental efforts have been made from time to time in the past fifty years to transplant free grafts of fascia for various purposes, but the first systematic study of the subject was made in 1909, by Kirschner. He found after many animal experiments, in which various layers of the abdominal wall were sacrificed, that he could prevent the development of hernias with free fascial transplants. After a great number of operations on man without a single case of disturbance of healing under aseptic conditions, Kirschner concluded that the heal-

ing tendency of fascia must be extraordinarily great to explain his large series of successes. He recognized the resistant quality of transplanted fascia even under the unfavorable circumstances of bad nutritional and septic conditions. Ordinarily, the graft would be subject to the cementing action of ingrowing connective tissue on both surfaces, but even when healing could occur on only one surface, such as when the graft faced the free peritoneal cavity, the result was successful. Furthermore, a transplant poorly nourished on both sides, such as one replacing the layers of the abdominal wall including peritoneum, and not covered by skin so that it was visible at every dressing, also remained viable. Dural defects could be grafted successfully even though one side is covered by bone and the other exposed to protein-poor cerebrospinal fluid. He cited one case, out of many, of fascial replacement of an abdominal defect secondary to a huge appendical abscess; this too was successful despite the presence of infection. Transplants under such conditions are not recommended, but such cases illustrate the extraordinary healing tendency of fascia.

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widely discussed. A large part of the experimental studies undertaken to settle this moot point must be ruled out because the periods of observation after transplantation are too brief. Permanent viability cannot be accepted as established since replacement phenomena and evidence of degeneration do exist. Experiments show that the general architecture of the graft is preserved for as long as six months to one year, but careful examination reveals the fact that the transplant is not preserved as such, but has been gradually replaced by fibrous connective tissue closely resembling it. That this replacement is very gradual is evident from the fact that the phenomena are not complete even after one year. This new tissue cannot be termed cicatricial, the resultant of degeneration, but may be more accurately described as a cellular connective tissue occupying the framework and largely maintaining the size and form of the original transplant. As a result, the purpose for which the transplantation has been performed can be ordinarily achieved. The ready transplantability of fascia and its great practical usefulness have been established on a firm basis.

#### THE FASCIA LATA

The fascia lata forms a uniform investment for the whole of the thigh but varies in thickness in different parts. The portion arising from the front part of the crest of the ilium, corresponding to the origin of the tensor fasciae femoris muscle, passes down the outer side of the thigh as two layers, one superficial to and the other beneath this muscle. At the lower end of the latter, which is about one-quarter of the way down the outer side of the thigh, these layers become blended into a broad thick band, which is continued downward to the knee. This iliotibial tract is the densest portion of the fascia lata and is the most desirable for transplantation. The histology of human fascia closely resembles that of the dog and rabbit, which are the experimental animals commonly used in work on this subject. Throughout most of its extent, it is composed of three layers. The fibers of the middle, the most dense and thickest of the three, run in the vertical axis while the fibers of the inner and outer layers course at right angles to the main median layer. Each of the strata is composed of closely woven bundles of wavy connective tissue, microscopically resembling tendon tissue. The median portion is joined to the inner and outer layers by loose connective tissue, which carries the blood vessels and most of the elastic fibers.

Fascia lata is superior to other similar tissues. It is easily accessible. Throughout its course it lies under the skin and a simple incision effects adequate exposure. It is readily freed from the subcutaneous fat and is easily detached from the underlying muscle, unlike the anterior rectus sheath with its tendinous intersections. The supply is plentiful even for the most extensive autoplasty. Especially is this true when both thighs are available. Successful grafts measuring nine inches square are not unusual. Its sacrifice is harmless. This does not hold when ab-

dominal fascia is used. Occasional herniation of the underlying muscle can be minimized or completely avoided if the margins of the defect in the fascia following excision of the patch are tacked down to the underlying muscle; spreading of the remaining defect is thus prevented. It has great strength combined with limited elasticity. Of the various fasciae in the human body, the fascia lata is the strongest, particularly in the iliotibial tract. Many clinical as well as experimental observations have established the fact that fascial grafts can withstand great strain. Kirschner found that whereas strips of periosteum were torn by a pull of thirteen pounds, a similar sheet of fascia lata supported a weight of ninety pounds. It exhibits an extraordinary tendency to heal in a viable state. It is readily adapted to the contours of all fields. There is no difficulty in suturing or fitting it into place.

#### APPRAISAL OF TRANSPLANT METHODS

Simultaneously with the evolution of the experimental phase of fascial transplantation, there developed its clinical application in a veritable host of conditions. Of interest to the orthopedic surgeon is its use in tendon defects, habitual dislocation of the shoulder, traumatic lesions of the capsule and ligaments of knee joints, flatfoot, and divided muscles such as ruptured biceps. The ophthalmic and plastic surgeons may use fascia in the treatment of paralyzed muscles as in ptosis and facial palsy. The neurosurgeon may consider its use in dural defects. The thoracic surgeon has patched pleural defects with fascia whether traumatic or postoperative, as following removal of sarcoma of the chest wall. Nephropexy by fascial strips is part of the urosurgeon's armamentarium. General surgeons are primarily interested in the use of fascial transplants in hernia and defects of the abdominal wall.

Ideal incisional hernioplasty demands an anatomic repair with free dissection and separate tier suture of all layers. This may be possible in the smaller hernias such as those following the McBurney incision. Avoidance of undue tension is the most important consideration for successful repair, since tension causes strangulation of the tissues with sloughing and failure of healing. Dickson has well expressed the importance of this factor: "It is much more important to direct effort to relieving wound tension than it is to devise some new type of suture material. A wound which is completely relaxed and without tension will have a good blood supply and no matter what suture material has been used, whether absorbable or nonabsorbable, or it might almost be said, whether any at all is used, the wound will heal."

Massive hernia with partially obliterated surrounding structures precludes anatomic repair. The number of operations that are ordinarily employed in the treatment of these cases is legion, and their very multitude is indicative of how frequently they fail; 25 to 40 per cent recur. There are many reasons for this. These cases present attenuated muscular and fascial structures with extensive scar tissue, often the re-

sult of repeated efforts to cure a postoperative hernia following infection, and such cases do not permit the ready approximation of healthy aponeurotic layers. Obesity and the generally poor physical condition of many of these patients add considerably to the risk of the operation. Under such conditions a minimal operative procedure is imperative, and yet with ordinary methods, repair of the defect would mean extensive plastic work on ill-nourished cicatricial tissues. Approximation of the edges of large defects may prove disastrous to the patient because of the sudden diminution in the size of the peritoneal cavity, which results in a disquieting increase of intra-abdominal pressure and a decrease in vital capacity. Because of this embarrassment, postoperative pulmonary complications are common. Pressure on the diaphragm produces cardiac symptoms from pressure on the heart and abdominal vessels. Acute gastric dilatation and ileus, too, are not uncommon complications. It is akin to ileus associated with a tight plaster spica and may occur whether or not the peritoneal cavity has been opened. These are the problems of hernioplasty which necessitate utilization of fascial transplants for safe and adequate repair.

The popular Gallie and Wangensteen procedures are developments of Kirschner's original and simpler patch transplantation. Both Gallie and Kirschner utilize free transplants, the former using the fascia as strips in the form of sutures. Wangensteen uses a pedicled transplant. It now behooves us to analyze the relative merits of these methods. Much light is thrown on this appraisal by a careful study of Gallie's experimental investigation as published in 1923. It was these observations which led Gallie to discard the patch transplant in favor of strips of fascia employed as interweaving sutures.

Gallie found that free transplants of fascia, whether in patches or suture strips, as well as pedicled transplants, lived unchanged when they could receive an adequate supply of lymph. This observation confirms the original work on the practicability of using free transplants of fascia. Since viability is established whether the transplant is pedicled or free, are the added technical manipulations that are part of Wangensteen's procedure at all necessary? There is no experimental evidence to prove that pedunculation of the graft ensures a greater degree of usefulness than the free graft; the value of preserving the blood and nerve supply is purely theoretical. There is no objection to using the pedicled transplant where it is readily applicable, but even Wangensteen admits that Kirschner's method of using a sheet of fascia lata as a free patch "permits of more universal application in the correction of tissue defects than the pedicled graft." For example, it may be impossible to adequately cover an upper abdominal defect with a pedicled graft, particularly in a patient with a short femur. Much of the available quantity of the graft is sacrificed by the waste entailed in covering the distance between the pedicle and the abdominal defect. This factor caused a

recurrence in one of the thirteen cases which comprised Wangensteen's original report. Another disadvantage is the possibility of obscured bleeding in the tunnel fashioned for transmission of the pedicled graft; this contrasts with the complete visualization which is always possible in using the free patch and this ensures perfect hemostasis. Finally from an aesthetic point of view, the patient occasionally objects to the cord-like bulge caused by the pedicle of the transplant and sometimes mistakes it for a recurrence of the hernia.

Gallie found that wounds in fascia, when sutured in edge-to-edge apposition with absorbable sutures, heal together by means of newly formed connective tissue which is not very strong and, if subject to strain, slowly stretches, leaving a gap between edges of the wound. He found that transplants heal to surrounding structures, by means of this delicate scar tissue, in exactly the same manner as healing of simple wounds in these tissues, and that it is the constant tendency of this scar to stretch, which explains the failure of many of the attempts which have been made to cure large hernias by the use of patch transplants. The reason for the stretching tendency of scar tissue is that, although composed of quite similar white fibers as fascia, these fibers are loosely and irregularly arranged in contrast to the parallel arrangement of the fibers in fascia which gives the latter great strength in the direction in which it is normally subject to strain. Gallie felt that he could overcome this objection by weaving the edges of the hernial defect together with the strips of fascia employed as everlasting living sutures. If approximation could not be obtained without disastrous increase in intra-abdominal pressure, Gallie originally suggested filling the gap with a living aponeurotic filigree by a basket weave of the fascial strips as in darning a sock.

At first glance one might feel that Gallie's findings doom the applicability of free patch transplants. However, we do not believe nature's process of healing wounds in aponeurotic structures to be as defective as Gallie was led to conclude. Certainly, the greatest number of laparotomy wounds heal satisfactorily with the ordinary method of suture. In those cases which do develop hernias it is everyone's experience that the latter develop soon after, or even before discharge from the hospital and not years later, as they should if stretching of the scar were the factor. Branch reported that in 46.3 per cent of 300 cases of incisional hernia, the patient noticed a mass in the wound ninety days or less after the original operation. To follow Gallie's thought to its logical conclusion, one would have to sew all laparotomy wounds with fascial suture strips. We feel that scar stretching is not the important factor in the development of postoperative herniation. More important considerations are careful closure, asepsis, and the use of incisions which cause the least trauma to muscles and nerves. Furthermore, Gallie admits that if the surfaces of the patch and surrounding tissue are thoroughly cleansed of areolar tissue, scarified and overlapped, they unite by a generous scar



and here the union is more solid and tolerates what may be considered normal degrees of strain. It is perfectly possible that it was the lack of proper cleansing and preparation of the sutured edges which accounted for the failures of some of the patch transplants, so that if these precautions are taken, uniformly good results may be obtained even without the use of Gallie's suture strips. One must bear in mind, too, that if scar stretching predisposes to failure in free transplants, this factor should apply equally in the Wangensteen pedicled transplant which is also sutured in place in the ordinary manner. And yet, the highly satisfactory results obtained with the Wangensteen procedure give cogent testimony to the successful use of transplants without fascial sutures.

Gallie found that gaping was less marked with linen than with catgut. We favor the use of silk in fixing the transplant. Since it is not absorbed, edge-to-edge apposition of transplant to environment is better maintained with a minimal tendency of stretching at the margins. Tension on the suture line is absent since the transplant method obviates the necessity of pulling the edges of the defect together, and, therefore, the sutures have no tendency to cut out. Parsons found that recurrences were four times as frequent in a series of inguinal hernias when catgut was used as when silk was employed. Whipple has shown that wounds repaired with silk were always superior in tensile strength to those repaired with catgut. Catgut caused greater trauma as well as pressure necrosis as evidenced by the zone of fluid and leucocytes surrounding the sutures.

The superiority of fascial sutures is not universally accepted. Branch reported 240 incisional hernias. Of this number, 226 repaired with fascial overlap and silk or catgut gave a recurrence rate of 19.6 per cent; 14 larger hernias were repaired by the Gallie method and of these 21.42 per cent recurred. Burdick, Gillespie, and Higinbotham reported on the use of fascial sutures in 1,485 hernias at the Hospital for Ruptured and Crippled. Their recurrence rate for 98 umbilical, epigastric, and ventral hernias was 44.89 per cent. Suppuration occurred in 7.9 per cent of the cases in which fascial sutures were autogenous. They no longer regard fascial strips as the suture material of preference and have turned to silk with better results. Gallie had to give up his filigree method of filling hernial defects because of a number of recurrences through the chinks between the sutures. He was forced to revert to the free patch transplant which he preferred to suture in place with fascial strips. His latest method is that of fixation of the patch by fashioning the latter into a many-tailed bandage design. We have not found it necessary to vary our technique at all since silk has been utilized.

A grave complication of the Gallie operation, which makes use of interweaving fascial sutures for pulling the defect margins together, is that of increased postoperative intra-abdominal pressure. Smith and Masson of the Mayo Clinic reported on the results of the use of the Gallie fascial

suture in 85 cases of ventral hernia. Four of their five postoperative deaths were due to pulmonary complications. Frequently it was necessary to place the patient in an oxygen tent immediately after operation. Power reported two cases of ileus following the Gallie operation, one of which terminated fatally.

The free patch transplant is not subject to many of the criticisms of the other plastic methods and its use deserves much more popularity. It is readily applicable to all cases. It does not have any of the limitations of the pedunculation method. It heals with a minimal reaction and is not associated with the suppuration not uncommonly present

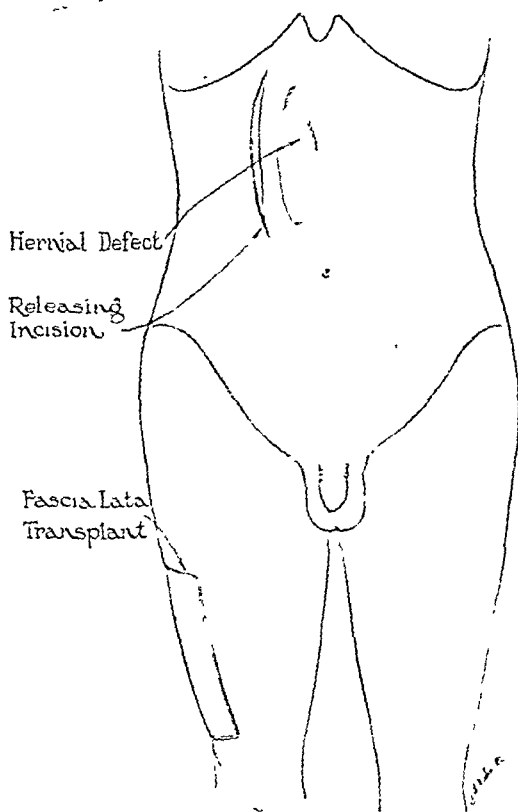


Fig. 1.—Releasing incision made through fascia on one side of hernial defect.

when fascial sutures are used. Proper preparation of the transplant and the recipient area as well as the use of silk technique ensures good healing and firm union. Wound tension and increased intra-abdominal pressure are completely avoided and this has been a primary consideration in our technique in applying the free patch.

#### INDICATIONS AND TECHNIQUE

The most important indication for using the fascial insert is a scarcity of satisfactory tissue about the hernial gap. Tissues that do not lend

themselves to adequate repair cannot be expected to withstand the great strain that would be put upon them, particularly with approximation under tension. Such a situation is often characteristic of recurrent hernia, large direct inguinal hernia, and massive abdominal hernia. Obviously, fascial transplantation is not indicated in every case of ventral hernia (Figs. 1, 2 and 3).

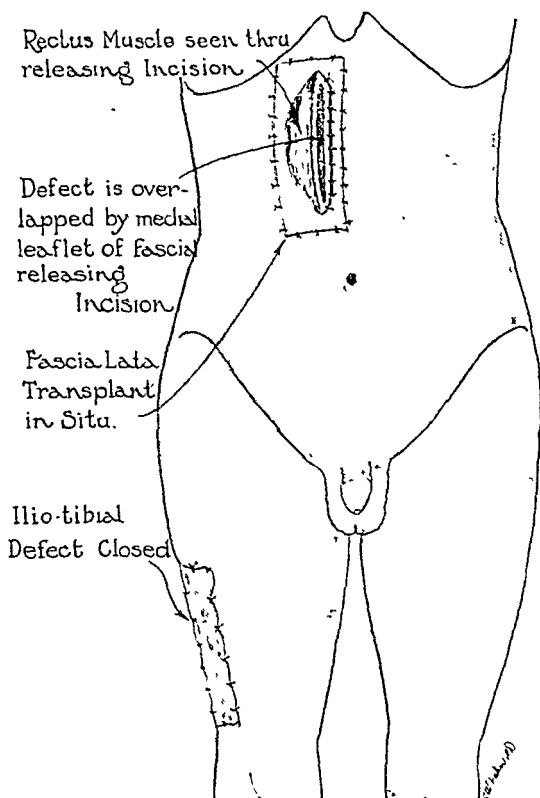


Fig. 2.—Original defect sutured, leaving a gap at the site of releasing incision. Graft overlies entire field, Iliotibial defect is closed by suturing margins to underlying muscle.

Simplicity keynotes the technique. The peritoneal cavity need not be opened and layer dissection of the abdominal wall is unnecessary, thus also effecting a great saving of time. The defect is exposed and the surrounding fascia is cleansed of all adherent areolar and scar tissue. A releasing incision is made on one side of the defect approximately one-half inch from the margin. The peritoneal bulge is depressed in the defect and the clearly defined margins are readily sutured with interrupted black silk without any tension. The line of the releasing incision in the fascia now gapes and exposes beneath it either the attenuated muscle layer or, frequently when this is absent, merely the posterior rectus sheath or transversalis fascia. An appropriately sized sheet of

fascia lata is excised from the ilio-tibial tract of the thigh and after being properly freed of its investing areolar tissue, it is sutured over the newly made defect with interrupted black silk sutures. A large enough graft may be taken to cover the primary suture line as well, thus effecting a wide margin of overlap with actual contact between the cleansed transplant and the freshened fascial surface. We have not found it necessary to use any drains. This method permits secure closure without producing the slightest tension and thus remains true to one of the most fundamental principles of surgery. In our opinion, it is superior to all suture methods, fascial or otherwise, which pull the margins of the defect together.

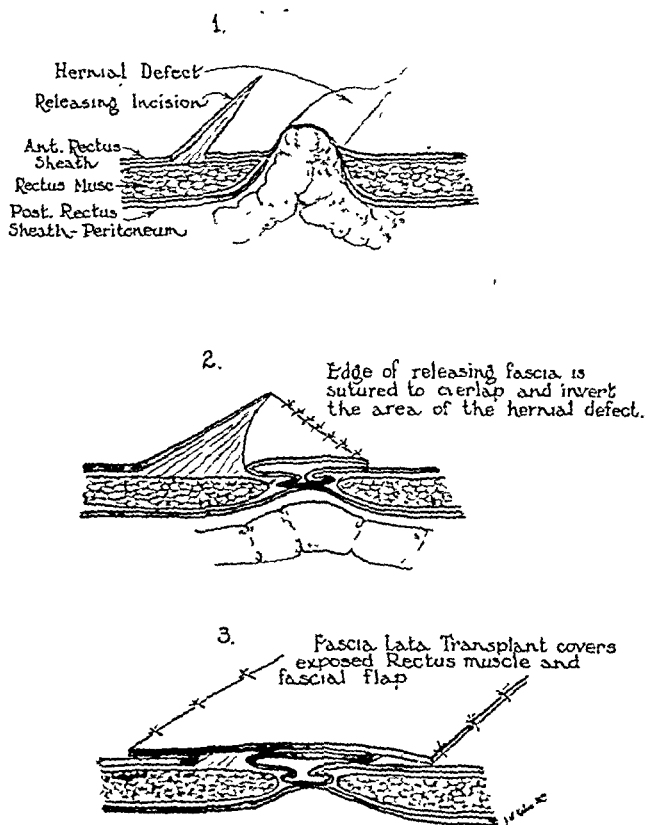


Fig. 3.—Schematic presentation showing the steps in the repair of the hernia.

At this writing, eleven cases of large ventral hernia have been operated upon at the Jewish Hospital of Brooklyn by this method, the first one three and one-half years ago and the last about two weeks ago. This is admittedly a small group with a relatively short follow-up. However, so completely uneventful have been their recoveries and so successful the results thus far, that one cannot help but be favorably impressed.

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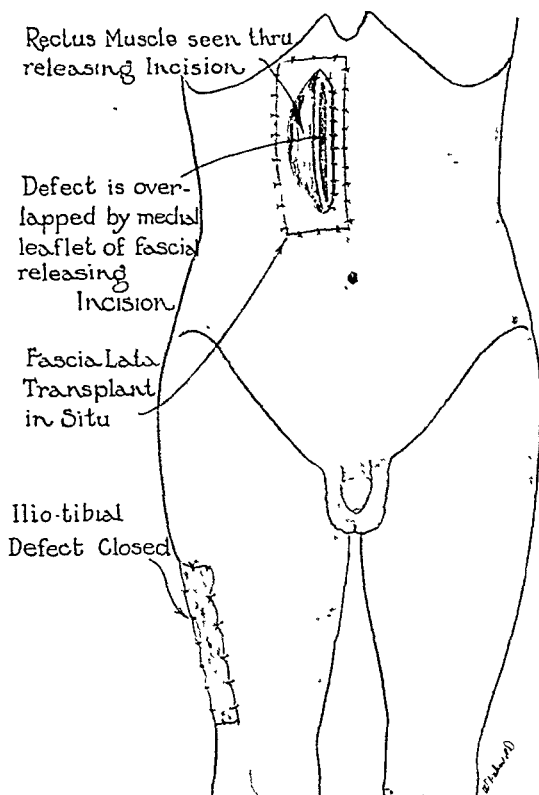


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## CONSIDERATION OF THE FACTORS INFLUENCING THE SURGICAL REPAIR OF INGUINAL HERNIA

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ONE person in ten, the world over, is afflicted with hernia. All ages of both sexes do not escape. Ninety per cent of all hernias are inguinal. Inguinal hernia is a foremost disabling condition in industrial workers and it ranks third in the causes of rejection for military service.

Operation for the cure of inguinal hernia is a common, everyday procedure in the modern hospital. It constitutes about 10 per cent of all types of surgery done in large general hospitals. Mortality rate is less than 1 per cent and morbidity from wound infection, pulmonary and other complications is, on the average less than 10 per cent. Recurrence of hernia, as generally admitted by surgeons at the present time, is seen in 5 to 10 per cent of the cases of which 80 per cent appear within the first year following operation. That an inguinal hernia once repaired results in a recurrence is evidence of an error, particularly when a second operation effects a permanent cure. The purpose of this discussion, therefore, is to consider the many factors which influence our judgment in the surgical treatment of inguinal hernia and review certain fundamental principles that will diminish the chance of error when properly applied.

### HIGHLIGHTS IN THE HISTORY OF HERNIOPLASTY

Hernia, a disease known to man since his beginning, has a story which is parallel with the history of medicine. Like so many other afflictions of mankind, rupture was an enigma through the centuries and attempts to solve its mystery by a multitude of methods were unfruitful. Credit for the first step in solving the problem of hernia is given the anatomists. Andreas Vesalius of the sixteenth century, and later Fallopius, Gimbernat, Scarpa, Cooper, and others, made discoveries in the anatomy of the inguinal region which proved to be most valuable in a fundamental understanding of inguinal hernia. The next step in unraveling the riddle of hernia was the discoveries which gave birth to the science of bacteriology and it was from Pasteur's work that Lister revolutionized surgery by the institution of his antiseptic methods in 1865. Oddly enough, the report of his first operation in 1869, using antiseptics, was a hernia case. Infection and suppuration, which had destroyed not only the surgeon's skillful work but frequently his patient as well, ceased to be the horrible result that had previously plagued the surgeon. Lister's antiseptic methods reduced surgical mortality to one-twentieth of the former rate. The enthusiasm of surgeons was manifest by the introduc-

It is the purpose of this paper to present the procedure at this time so that others may be stimulated to use it in the interest of amassing a larger group of cases for a more fully tested appraisal.

### SUMMARY

The fact that one can with impunity make an autogenous transplant of fascia lata is now well established. Kirschner was the first to crystallize the method into a sound surgical procedure. The disputed question of ultimate viability of the transplant is only of academic importance. Fascia lata of the iliotibial tract is the most desirable for transplantation. Free patch transplantation of fascia deserves more popularity, since in many ways it is superior to the Gallie and Wangensteen procedures. A technique for the use of the free transplant in the surgery of large incisional hernia is described.

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tion of fibrous tissues in the repair of anatomic defects by using fascia lata strips as suture material and graft. Pitzman,<sup>1</sup> in the same year, stressed the importance of repair of defects in the transversalis fascia. Seelig and Chouke,<sup>12</sup> in 1923, by experiments in dogs showed that muscle sutured to fascia resulted in poor union and suggested that fascial structures be sutured to fascia for the best results in the treatment of hernia. In 1934, Wangenstein<sup>13</sup> presented a new application of an established principle in plastic surgery, the transplantation of a musculotendinous structure, the iliotibial tract, with its nerve and blood supply intact swung up from the thigh into defects of the abdominal wall. Anson and McVay,<sup>14</sup> in 1938, by careful studies of the anatomy of the inguinal region, pointed out important relations of the muscle and fascia, and McVay, in 1939,<sup>15</sup> on the basis of these new investigations discussed a fundamental error in the Bassini operation in that the inguinal ligament does not withstand very well the pull exerted by muscles sutured to it and suggested that better results could be obtained by the suture of the inferior aponeurosis of the transversus abdominis to the fibrous covering of the pubic pecten as far laterally as the femoral vein. Anson and McVay have contributed a great deal toward the improvements that may be made in the operative repair of inguinal hernia.

#### REDUCTION OF THE RECURRENCE RATE

Since Halsted<sup>4</sup> once stated that "the cure of hernia may be listed with the triumphs of surgery," the surgical treatment has in many respects come a long way. Nevertheless, hernial surgery is far from perfect as the evidence of recurrences will bear out. Recurrent hernia in the narrowest sense implies the return of exactly the same type of hernia as existed before operation. True recurrences are relatively rare and the designation "recurrent" embraces all types of inguinal protrusions occurring after a hernioplasty. Recurrence rate among surgeons varies considerably as some quote a rate as high as 25 per cent, particularly in direct hernia, and others as low as 0.8 per cent (Joyce<sup>16</sup>). Undoubtedly, the personal equation plays a part. Error in technique of the original surgeon or the use of a technique not suitable for the adequate repair of the type of hernia that exists is a suggested explanation for later development of a weakness in the inguinal region that is characterized as a "recurrence." As Fallis<sup>17</sup> has stated, "improvement in results of hernial repair will not come from inventing new operations, but from carefully following certain well-defined principles which now yield excellent results when properly applied." To repeat that hernial surgery is not perfect, therefore, may be interpreted also as meaning that principles we have already learned in the surgical treatment are oftentimes not properly applied.



tion of a multitude of operations for hernia which were as numerous as the surgeons doing them. Controversy over antisepsis and asepsis soon arose but Lucas-Championnière pointed out that boiling and heat sterilization were in the true sense antiseptic though without the disadvantages of chemical antisepsis. He was the first to operate under aseptic precautions. With so many different methods attempted in the surgical treatment of hernia, there were many recurrences of hernia and it was obvious that there was a need for improvement in the technique. This came as another great step with the introduction of the Bassini<sup>2</sup> and Halsted<sup>3</sup> methods of hernia repair. The techniques were developed independently and reported at about the same time, 1890. Halsted<sup>4</sup> later changed his original technique so that the essential difference from the Bassini method was in relation to the spermatic cord. Bassini reconstructed the tissues posterior to the cord, transplanting it anteriorly, whereas, Halsted reinforced the tissues anterior to the spermatic cord. Strange as it may seem, these two methods have been the basis of operative repair of hernia to this day. All operations introduced have been modifications of these two original methods. New additions to the operative treatment of hernia have been made during the past fifty years and the operative technique of surgery in general has been greatly refined by knowledge gained from researches in the basic sciences as well as the surgical skill manifested by the masters of the art. Among the outstanding contributors to hernia surgery since 1890 are Wolfer,<sup>5</sup> who in 1892 suggested the use of the rectus muscle or its sheath as a reinforcement of Hesselbach's triangle, and Bloodgood<sup>4-6</sup> in the same year sutured a triangular flap of the rectus sheath to the inguinal ligament for the same reason. Andrews,<sup>7</sup> in 1895, described a method of imbrication of the layers of the abdominal wall in which the transversalis, internal and external oblique muscles were sutured as one layer over the cord to Poupart's ligament and the lower flap of the external oblique was carried up over the upper flap and sutured to it. This was an advancing step in the treatment of direct hernia. In 1899, Ferguson<sup>8</sup> closed the transversalis fascia tightly over the cord and made the internal abdominal ring smaller. McArthur,<sup>9</sup> in 1901, suggested the use of the edge of the external oblique aponeurosis as a living fascia suture to unite the muscle to the inguinal ligament. In 1919, LaRoque<sup>1</sup> devised an intraabdominal removal of the hernial sac followed by the plastic repair of the inguinal structures. Hoguet,<sup>10</sup> in 1920, advised opening the hernial sac near the internal inguinal ring in the repair of direct inguinal hernia, a definite advance in the surgical technique in which the direct hernial sac is converted into an indirect sac by traction on the opened peritoneum at the internal abdominal ring and dissection of the preperitoneal structures from it. Gallie and Le Mesurier,<sup>11</sup> in 1921, described the transplanta-

of the peritoneum at the internal ring as suggested by Fallis and McClure.<sup>18</sup> The sac should be closed at the internal abdominal ring. This may be accomplished by a continuous or purse-string suture if the opening is large or by twisting the neck of the sac and applying a transfixion suture if it is narrow. Upon excision of the sac after the closure, the stump will retract high because the peritoneum was previously drawn fairly taut. The choice of reconstruction of the inguinal region depends upon what one has found to be at fault in the supporting structures of this region. A standard operation to be used in the repair of all inguinal hernia is as impractical as a one for all procedure in any other type of surgery. Principles come to play as much importance in the repair of a hernia as in the proper correction by surgical methods of other conditions. The importance of carefully repairing weaknesses of the transversalis fascia in inguinal and femoral hernias is a step that must not be overlooked. Very often the weakness or separation of the fibers can be repaired by interrupted or plicating sutures. Where the weakness is a large one, due to wide separation of fibers, congenital absence, or atrophy, then a substitute must be made to reinforce the weakened site by the use of fascia as suggested by Gallie or the transplantation of a flap according to Wangenstein's method. The femoral opening in femoral hernia may be repaired by suturing the transversalis fascia to Cooper's ligament as suggested by Dickson.<sup>19</sup> To omit the repair of the transversalis fascia or to fail to apply a substitute for it is a grave error in technique and one of the chief causes of the "recurrence."

Considerable controversy has attended the wisdom of transplantation of the cord. There are those who believe that a weakness is produced at the internal abdominal ring by this step and others state that the lower inguinal region is weakened by omitting it. Here again, the choice may be made by the consideration of the facts. Gallie's statement in disagreement with the proponents of methods of repair anterior to the spermatic cord, "the time which is spent in preventing a hernia from getting out of the inguinal canal is much better spent in preventing it from getting in," is a point in favor of those methods used to repair and reinforce the structures posterior to the cord. Where there is a well-developed weakness through Hesselbach's triangle (direct hernia) and an additional support is desired over this point, the cord should be transplanted in order to conveniently suture fascial structures to fascial structures in this region. As Anson and McVay have pointed out the undesirable results of suturing muscle or fascia to Poupart's ligament, it is better to suture the inferior aponeurosis of the transversus abdominis to the pubic pecten and the insertion of the tendon of the rectus abdominis to the point of insertion of the inguinal ligament at the spine of the pubis. In addition, the corresponding portions of the aponeurosis of the internal oblique may be sutured to the pubic pecten. This accomplishes a firm reinforcement of the lower inguinal

MANEUVERS IN TECHNIQUE CONTRIBUTING TO THE EASE AND  
THOROUGHNESS OF THE REPAIR

All hernia operations have followed certain general principles, namely, high ligation and excision of the sac, and second, plastic reconstruction of the inguinal canal. At operation, an examination of the tissues is the first step in planning the repair. Anatomic structures vary in strength and development in different individuals and obese patients frequently offer the most difficult problems. Long standing, large hernias are often accompanied by distortion and atrophy of structures essential for use in the reconstruction. Inguinal hernia in the extremes of life gives a different picture, for in the child anatomic changes to the extent of almost complete destruction have not occurred and the tissues are in a state of growth as compared to the state of degeneration in the elderly person. Depending upon the condition of the tissues, large hernias may or may not be more difficult to repair than small hernias. The accurate diagnosis of the type of hernia with which one is dealing is the next step. This can only be made by opening the peritoneum at the internal ring, introducing the examining finger through this opening into the peritoneal cavity, and testing with the finger the usual sites of exit of a peritoneal pouch such as Hesselbach's triangle and the femoral ring. Femoral hernia is in the true sense a type of inguinal hernia and is often missed entirely by omitting this important step. Failure to recognize the presence of a double sac or the saddlebag (direct-indirect) type of hernia is a principal cause of recurrence. This is likely to happen when only a small indirect hernial sac is discovered and the surgeon is less careful with repair of the small hernia than a large one. Direct hernias rarely, if ever, strangulate, but incarceration and strangulation are common in indirect and femoral hernias. The careful inspection of bowel or omentum contained within a hernial sac is the most important part of the operation and may necessitate a second incision through which the extraction, examination, and repair of the bowel is done, leaving the repair of the hernia as a step, second in importance. Most inguinal hernias contain omentum which is unattached to the sac and slips readily into the peritoneal cavity. In every operation for inguinal hernia, the loose, redundant peritoneum should be carefully withdrawn through the internal abdominal ring as the preperitoneal structures are wiped aside with the gauze-covered finger. It is surprising in many cases the amount of peritoneum that one can recover by this maneuver. That the step has a decided advantage is noted by the smoothing out of the peritoneum covering the openings from the abdominal cavity and rendering relatively loose the transversalis fascia over and about these openings making the fascia easier to repair later in the operation. As both a femoral and inguinal hernia may be present at the same time, both may be repaired by bringing the femoral sac through the opening

of the peritoneum at the internal ring as suggested by Fallis and McClure.<sup>18</sup> The sac should be closed at the internal abdominal ring. This may be accomplished by a continuous or purse-string suture if the opening is large or by twisting the neck of the sac and applying a transfixion suture if it is narrow. Upon excision of the sac after the closure, the stump will retract high because the peritoneum was previously drawn fairly taut. The choice of reconstruction of the inguinal region depends upon what one has found to be at fault in the supporting structures of this region. A standard operation to be used in the repair of all inguinal hernia is as impractical as a one for all procedure in any other type of surgery. Principles come to play as much importance in the repair of a hernia as in the proper correction by surgical methods of other conditions. The importance of carefully repairing weaknesses of the transversalis fascia in inguinal and femoral hernias is a step that must not be overlooked. Very often the weakness or separation of the fibers can be repaired by interrupted or plicating sutures. Where the weakness is a large one, due to wide separation of fibers, congenital absence, or atrophy, then a substitute must be made to reinforce the weakened site by the use of fascia as suggested by Gallie or the transplantation of a flap according to Wangensteen's method. The femoral opening in femoral hernia may be repaired by suturing the transversalis fascia to Cooper's ligament as suggested by Dickson.<sup>19</sup> To omit the repair of the transversalis fascia or to fail to apply a substitute for it is a grave error in technique and one of the chief causes of the "recurrence."

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region and transplants the cord to some extent. Where the weakness was chiefly at the internal inguinal ring, through which a large indirect sac escaped, the ring may be reinforced and narrowed by drawing together the fibers of transversalis fascia about it and the cord need not be transplanted. Where weakness was present at the internal ring, Hesselbach's triangle, and the femoral ring, steps which have been suggested may be taken to repair and strengthen all of these sites at the same operation. To me it seems that a surgeon cannot really plan his operation in the treatment of inguinal hernia any more so than he can an operation within the abdomen until he has actually made the incision and carefully examined the structures he is to deal with.

#### THE SELECTION OF SUTURE MATERIAL

The repair of inguinal hernia is, in most instances, a clean wound procedure as well as a problem in plastic surgery. Adherence to rules governing clean wound repair is of primary importance in hernial repair. Whipple<sup>20</sup> has carefully enumerated the factors of clean wound repair and healing and has placed particular emphasis on the choice of suture and ligature material.

Since Halsted<sup>21</sup> introduced the silk suture into American surgery in 1882, its use has become increasingly popular. His pupils became masters in the silk technique and are responsible for the place it holds in our best American clinics. Kocher,<sup>1</sup> in Berne, first discovered advantages of silk and Halsted later established the principles for its successful use, which have withstood the test of time as one of the great advances in surgical technique. He remarked that "the surgeon wedded to catgut is deprived of useful devices which become indispensable and a delight to the surgeon who has acquainted himself with the possibilities of silk."

The use of the silk technique stimulated the study of the effect of various suture and ligature materials in wounds and their influence upon the healing of wounds. One of the chief reasons Halsted substituted silk for catgut was that catgut was a source of infecting organisms. The present day preparation of surgical gut has eliminated the possibility of its contamination but it is known to favor growth of organisms introduced at the time of operation. Some arguments on this score may be mentioned. The length of time surgical gut remains intact and strong enough to retain anatomic structures in their position is not definitely known. Although finer strands of surgical gut with stronger tensile strength are now available, they cannot be entirely depended upon to fulfill the requirements. The strands of catgut to match silk in relative tensile strength must be larger and thus more material is left in the wound. Larger needles are required for their introduction and thereby surgical trauma to the tissues is increased. To adequately secure knots in surgical gut, the knot must be tied with greater force and the cut ends left longer to prevent the knot from

slipping. Chemicals used in the sterilization of surgical gut as well as the catgut itself tend to produce reactions in tissues. Meleney<sup>22</sup> showed the superiority of silk to catgut by proving less infections and more complete hemostasis, as well as ease of sterilization. He stated that the change from catgut to silk had proved to be the more important factor in the reduction of wound infection. Reid<sup>23</sup> has stated, "Non-absorbable material is preferred in the ligation of blood vessels as catgut may become absorbed or stretch too rapidly, which is especially true when infection is present." Kraissl<sup>24</sup> has discussed suture material on a comparative basis and concluded that better general results are obtained when silk is used. Meade and Ochsner<sup>25</sup> in a similar study of suture materials reached similar conclusions concerning catgut and nonabsorbable sutures and showed the merits of silk and cotton thread to be desirable in repair of wounds. Howes,<sup>26</sup> Shambaugh,<sup>27</sup> Localio and Hinton,<sup>28</sup> Kaufman, Johnson, and Lesser,<sup>29</sup> and Burdick, Gillespie, and Higginbotham<sup>30</sup> have offered rather convincing comment on the subject of suture material to be used in hernial surgery. Ramos and Burton,<sup>31</sup> Zimmerman,<sup>32</sup> Parsons,<sup>33</sup> and Stein and Brown<sup>34</sup> have recently shown with supportive evidence the value of silk in the repair of hernia. It may be obvious, therefore, that the sutures and ligatures to be used in the repair of hernia must satisfy certain requirements. Although the ideal suture has not yet been discovered, it is wise to accept and use the suture material which will best retain the structures in their place until healing is complete if the recurrence of hernia is to be avoided.

#### IMPORTANCE OF THE ANESTHETIC

It is not easy to render a careful and accurate repair of an inguinal hernia if the tissues are not well relaxed. A well-chosen anesthetic to meet this requirement is essential. The agents available for this purpose are now relatively safe, particularly in the hands of trained anesthetists. The choice of anesthetic is immaterial so long as it is safe, renders complete relaxation, and is not prolonged beyond its usefulness for too long a time.

#### POINTS IN THE PREOPERATIVE PREPARATION AND POSTOPERATIVE CARE

In hernial surgery as in surgery in general, careful preoperative preparation of the patient as well as postoperative care contribute to the safety and comfort of the patient and the success of the operation. Except for the emergency of strangulation, hernial operation is one of election. Ample time may be taken to decrease the weight of the obese patient or to improve the nutrition of a debilitated one and thus put the tissues in their best condition. Time so taken will pay dividends. The average time required for a wound to completely heal by first intention is about thirteen days, possibly a bit less in youth and somewhat longer in the aged. It does not seem wise to allow a patient

TABLE I

SUMMARY OF THE TYPES OF HERNIA, METHODS OF REPAIR, AND THE RECURRENCES

	ANTERIOR TO CORD REPAIR; MODIFIED HALSTED TECHNIQUE	POSTERIOR TO CORD REPAIR, MODIFIED BASSINI TECHNIQUE	RECURRENCE OF HERNIA AFTER HALSTED REPAIR	RECURRENCE OF HERNIA AFTER BASSINI REPAIR
Indirect hernia	15	13	0	1 (direct)
Direct hernia	1	27	0	1 (indirect)
Bilocular hernia (direct indirect)	0	11	0	0
Recurrent hernia	0	3	0	0
Total	16	54	0	2

Bilateral hernia was present in 26 patients. Both sides were repaired at the same time.

TABLE II

THE CASES IN WHICH RECURRENCES WERE FOUND

HENRY FORD HOSPITAL	ORIGINAL HERNIA	TECHNIQUE (YEAR)	RECURRENCE DISCOVERED	TYPE OF RECURRENCE	SECOND OPERATION
No 208899	Bilateral indirect	Halsted, right Bassini, left Dec 24, 1934	1941	Small direct hernia, left side	April 4, 1941
No 219727	Bilateral direct	Bassini technique both sides July 18, 1935	1936	No true hernia, fat pad in the cord mistaken for small sac	March 17, 1936

Both recurrences followed bilateral hernioplasties.

TABLE III

DATA IN THE ONLY CASE OF WOUND INFECTION

PREOPERATIVE SKIN PREPARATION	TOTAL TIME OF OPERATION	SUTURES USED	POSTOPERATIVE HOSPITALIZATION	END RESULT
Tincture of mercuric iodine	40 min.	Silk	18 days	Cultured organism Staphylococcus, small draining sinus for two months, no recurrence, 15 months

TABLE IV

POSTOPERATIVE PULMONARY COMPLICATIONS IN RELATION TO ANESTHESIA USED

	BRONCHITIS	PULMONARY ATELECTASIS	PNEUMONIA	INFECTATION	EMBOLISM	END RESULT
Ethylene and ether	0	0	0	1	0	Recovery
Avertin and ether	0	0	0	0	0	
Ether alone	0	0	0	0	0	
Spinal (Spinocaine)	0	2	0	1	0	All recovered
Total	0	2	0	2	0	

Spinal anesthesia used in 50 patients.  
Inhalation anesthesia used in 24 patients (ethylene with ether 12, avertin-ether, ether, 8).  
Local (novocain) not used in any of the cases of this series.

on his feet before his wound has been allowed to firmly heal. Some surgeons are anxious to get the patient up and about as soon as possible with the idea that he will maintain his strength and muscle tone and diminish the possibility of thrombosis and pulmonary complications. The therapeutic value of rest is not to be overlooked and a wound heals kindlier with rest than when the structures about it are put to work. Immobilization and rest of wounds not only diminishes the chance of infection but also results in a more rapid healing, as the methods of Orr<sup>35</sup> and Trueta<sup>36</sup> have shown.

The patient's occupation may be the factor to determine the length of time he is allowed to convalesce after a hernial operation. A patient whose duties require less vigorous activity, such as office work, may return to work at three weeks from the day of operation, whereas, the hard laborer should be given four or five weeks to fully regain his normal strength. This is a matter, however, which is flexible between patient and doctor, for it is doubtful if the recurrence of hernia has any bearing upon how soon the occupation is resumed if the hernia was properly repaired and the wound completely healed.

#### STATISTICAL STUDY OF 100 HERNIOPLASTIES

Statistical studies in a group of hernia cases are of greater value when made in a sufficiently large collection over an extended period of time. Seldom does such a study give all the facts that should be known to make it entirely accurate, for in clinical surveys many obstacles, over which one has little control, enter into the picture. The matter of keeping records is not difficult, but it is perplexing if the patient does not cooperate and return at intervals for the follow-up examination.

To eliminate to some extent the inaccuracy of a study of consecutive cases of hernia, I have not included those patients who failed to report after six months. A group consisting of 74 male laborers, in whom 100 operations for inguinal hernia was performed by me between the years 1934 to 1940, is submitted for analysis. The ages varied between 18 to 58 years. All the patients responded to recall for one year or more.

#### OTHER COMPLICATIONS

1. Atrophy of left testis in one patient, aged 45 years. Bassini operation was performed on both sides in repair of bilateral direct hernias.
2. Swelling of left testis without apparent atrophy in one patient, aged 53 years. Modified Halsted operation was done for repair of an indirect hernia.
3. Thrombosis of the femoral vein with tenderness and swelling of the lower extremity. No patients showed definite signs.

#### SUMMARY OF DATA

1. One hundred operations for inguinal hernia in 74 male laborers were performed between 1934 and 1940.



2. The cases are not consecutive, but include only those patients with in this six-year period who returned for follow-up for one or more years.

3. There were 84 modified Bassini operations and 16 Halsted or anterior to the cord repairs.

4. There were two recurrences, both following Bassini repairs. A direct hernia appeared after a repair of an indirect in one case of bilateral herniotomy. The other was not a true recurrence but must be considered one technically because a large mass of fatty tissue in the cord protruded through the external ring and gave the impression of a hernial sac. The results were established at the second operation.

5. There was one case of wound infection, with a draining sinus. In this case the wound ceased to discharge after two months and remained healed for fifteen months, which was the total length of time this case was followed. When last seen there was no evidence of recurrence of hernia.

6. There were four cases of postoperative pulmonary complications from which all recovered. In one case, there was pulmonary infarction, proved by roentgenogram, following an inhalation anesthetic. Two cases of pulmonary atelectasis and one of pulmonary infarction, proved by roentgenogram, followed spinal anesthetics.

7. Spinal anesthesia was used successfully in 50 patients and an inhalation anesthetic in 24.

8. The silk technique was used in 99 operations and in one case cotton thread was substituted for silk. Since all these cases were elective, clean wound subjects, surgical gut was avoided.

9. Although there were two proved cases of postoperative pulmonary infarction, in neither case was thrombosis of the femoral vein manifested by pain or swelling in the lower extremities. The patients were discharged from the hospital on the twenty-second and twenty-ninth postoperative days respectively.

#### COMMENT

In this study, emphasis is placed on recurrence of hernia and factors to avoid it.

The recurrence rate of 2 per cent in this series is low and cannot be taken as a rate representing consecutive cases. More material is on hand in a study of consecutive patients but less accuracy is afforded in concluding the recurrence rate. Data taken on patients never seen after one or two months is worthless in calculating a recurrence rate. Bilateral operations are of economic value but recurrences are increased as well as complications.

Infection occurred in 1 case, or 1 per cent, in this series. The cause was suspected by discovery that silk sterilized and stored away for a few days had been used in the operation. No infections occurred be-

fore or since this event when silk or cotton thread was boiled for twenty minutes immediately before use. This point seemed to be an explanation in our case, although many avenues of contamination may be suspected as the cause of an infected wound.

Swelling and atrophy of the testis is the result of trauma to it and the spermatic cord as well as strangulation of its circulation. It may be avoided by gentle dissection and especial care in reconstructing the tissues about the internal and external inguinal rings. Overlapping of the aponeurosis of the external oblique muscle should not exert too great pressure on the cord.

Phlebothrombosis and thrombophlebitis accompanied by pulmonary infarction and embolism are complications which are infrequent. When they occur, they are potential dangers to the life of the hernia patient. One should be constantly on the alert for their early signs. It is as important to prevent them as to treat them. Operative gentleness to the tissues and complete hemostasis certainly contribute to the prevention as much as postoperative precautions. The early use of heparin in the treatment of these complications has been a lifesaving measure.

#### SUMMARY

The incidence of inguinal hernia and the frequency of herniotomy in modern hospitals is cited to emphasize the relative importance the disease displays in the human economy.

As a basis for the discussion of fundamental factors influencing the treatment of inguinal hernia, the highlights in the history of hernial surgery are briefly reviewed.

Although the cure of hernia is a triumph of surgery, the surgical treatment is by no means perfect as is illustrated by so-called "recurrences."

True recurrence, or the return of the exact type of hernia that existed before operation, is rare. The "recurrence" usually represents all types of inguinal protrusions that occur after hernioplasty. Reduction in the rate of recurrence may come from following well-defined principles now yielding good results when properly applied, rather than invention of new operations.

Technical steps, which contribute to the ease and thoroughness in the repair of inguinal hernia, are recalled. These steps constitute maneuvers suggested by the trail blazers in the art of hernial surgery. They are worthwhile in diminishing technical errors and this is reason enough to adopt their use.

Hernioplasty is in most cases an elective, clean wound procedure. Adherence to rules governing clean wound repair are of primary importance. The silk or cotton thread technique is within this realm and the laws for its successful use are strict, but the results obtained are the surgeon's delight.

2. The cases are not consecutive, but include only those patients with in this six-year period who returned for follow-up for one or more years.

3. There were 84 modified Bassini operations and 16 Halsted or anterior to the cord repairs.

4. There were two recurrences, both following Bassini repairs. A direct hernia appeared after a repair of an indirect in one case of bilateral herniotomy. The other was not a true recurrence but must be considered one technically because a large mass of fatty tissue in the cord protruded through the external ring and gave the impression of a hernial sac. The results were established at the second operation.

5. There was one case of wound infection, with a draining sinus. In this case the wound ceased to discharge after two months and remained healed for fifteen months, which was the total length of time this case was followed. When last seen there was no evidence of recurrence of hernia.

6. There were four cases of postoperative pulmonary complications from which all recovered. In one case, there was pulmonary infarction, proved by roentgenogram, following an inhalation anesthetic. Two cases of pulmonary atelectasis and one of pulmonary infarction, proved by roentgenogram, followed spinal anesthetics.

7. Spinal anesthesia was used successfully in 50 patients and an inhalation anesthetic in 24.

8. The silk technique was used in 99 operations and in one case cotton thread was substituted for silk. Since all these cases were elective, clean wound subjects, surgical gut was avoided.

9. Although there were two proved cases of postoperative pulmonary infarction, in neither case was thrombosis of the femoral vein manifested by pain or swelling in the lower extremities. The patients were discharged from the hospital on the twenty-second and twenty-ninth postoperative days respectively.

#### COMMENT

In this study, emphasis is placed on recurrence of hernia and factors to avoid it.

The recurrence rate of 2 per cent in this series is low and cannot be taken as a rate representing consecutive cases. More material is on hand in a study of consecutive patients but less accuracy is afforded in concluding the recurrence rate. Data taken on patients never seen after one or two months is worthless in calculating a recurrence rate. Bilateral operations are of economic value but recurrences are increased as well as complications.

Infection occurred in 1 case, or 1 per cent, in this series. The cause was suspected by discovery that silk sterilized and stored away for a few days had been used in the operation. No infections occurred be-

fore or since this event when silk or cotton thread was boiled for twenty minutes immediately before use. This point seemed to be an explanation in our case, although many avenues of contamination may be suspected as the cause of an infected wound.

Swelling and atrophy of the testis is the result of trauma to it and the spermatic cord as well as strangulation of its circulation. It may be avoided by gentle dissection and especial care in reconstructing the tissues about the internal and external inguinal rings. Overlapping of the aponeurosis of the external oblique muscle should not exert too great pressure on the cord.

Phlebothrombosis and thrombophlebitis accompanied by pulmonary infarction and embolism are complications which are infrequent. When they occur, they are potential dangers to the life of the hernia patient. One should be constantly on the alert for their early signs. It is as important to prevent them as to treat them. Operative gentleness to the tissues and complete hemostasis certainly contribute to the prevention as much as postoperative precautions. The early use of heparin in the treatment of these complications has been a lifesaving measure.

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## INTESTINAL CAPILLARY CIRCULATION DURING DISTENTION

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RECOVERY of normal activity in obstructed and distended intestine is possible after many hours.<sup>1, 2</sup> The mortality rate of distention is associated intimately with the degree of embarrassment of the blood supply to the affected portion of the bowel.<sup>3</sup> The question of viability of the intestine<sup>4</sup> is important and the present study was undertaken to determine the role of the intestinal capillary circulation during varying degrees of intraluminal pressure.

### METHOD

Rats anesthetized with pentobarbital sodium subcutaneously (4.5 mg. per 100 Gm. rat) were used. A fourth of this dose was repeated hourly as needed. A 2 cm. piece of intestine (jejunum or ileum), drawn out through an abdominal stab wound, was distended with air and illuminated without heating<sup>1, 2</sup> (Fig. 1), but with blood supply intact. Capillary circulation was observed at a magnification up to 150 diameters.

The field under observation and all exposed viscera were kept covered with a gentle stream of mammalian Ringer's solution at 38° C. The rat itself was supported on a warm stage, also at 38° C. It proved important to prevent angulation or kinking of the vessels supplying the distended loop. This factor was controlled uniformly.

Careful hemostasis was observed throughout. The ligatures holding the cannula for air pressure and the quartz rod light source (Fig. 1) were placed so that the blood supply to the loop of intestine under consideration was not interrupted. A loop was chosen so that it was supplied by both limbs of a mesenteric arterial arcade of vessels.

Controls with loops prepared as described but without distention did not show any change of capillary circulation up to five hours. This controls the factor of necessary exposure.

Illumination within the intestine was furnished by a modification of the Knisely technique<sup>4</sup> as described by Wakim and Mann.<sup>5</sup>

Two series of experiments were performed: (1) increasing degrees of distention for short periods (two minutes) to determine the level at which intraparietal capillary flow was changed or stopped; (2) increasing time periods during which the intestine was maintained at a fixed distending pressure. Capillary circulation was observed during and at the end of this second series of experiments up to thirty to sixty minutes after deflation.

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## RESULTS

*Description of the Capillary Field.*—In any field examined at the anti-mesenteric border under a magnification of 75 to 150 diameters (Fig. 2) several arterioles and venules were seen accompanying one another, each pair lying only approximately at right angles to the long axis of the gut. The capillaries may be seen issuing from the arterioles. They always arise from their vessel of origin so as to lie either strictly in the long axis or at 90 degrees to the long axis. Thus the typical capillary pattern, as seen, described a series of rectangles (the sides of which were often at different levels) which overlay or underlay the larger vessels. This pattern is especially evident when for any reason the capillaries are dilated (reactive hyperemia) or when they contain motionless erythrocytes (excessive intraluminal distending pressure).

Continuous examination of any field made it quite evident that the smallest vessels were of two kinds, one which always was carrying blood and another which showed only an intermittent flow. Both types showed plasma skimming.

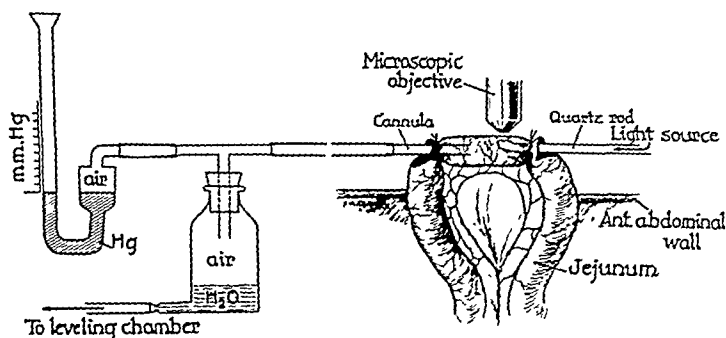


Fig. 1.—Experimental assembly for visualizing intraparietal intestinal circulation during intraluminal distention.

When the circulation through capillaries was viewed within a lymph aggregate, the usual pattern of distribution was not seen. No definite plan of distribution could be distinguished within the node.

*Intraluminal Pressures at Which Intestinal Intraparietal Capillary Circulation Is Altered.*—At distending pressures of 10 and 20 mm. of mercury the intestine was more transparent than before distention but no changes of circulation were noted. At 30 mm. the capillary circulation was at first a little slower, then faster again, as was the circulation in the arterioles and venules. Individual erythrocytes could be identified. At 40 mm. a few capillaries disappeared and a few more contained motionless erythrocytes, but most were normal. Flow in arterioles and venules was slower. At 50 mm. only a few capillaries were patent. Some larger vessels contained oscillating cells while the largest still had rapidly flowing blood. At 60 mm. all capillary flow had ceased and only in the largest vessels was blood flowing rapidly.

At 70 mm. no flow at all was seen except in one or two large vessels (arterioles and venules) which had a sluggish or oscillating flow and at 80 mm. even this had stopped.

At each distending pressure up to 50 mm. of mercury the rate of flow immediately after establishment of the new level was slower than previously but within one minute it was faster again. At the end of any series when the distending pressure was released, intense hyperemia was seen, the so-called reactive hyperemia. Functioning capillaries were dilated widely. The typical capillary pattern was thus quite clear and many capillaries could be seen that had not been in evidence before. This hyperemia lasted less than one minute.

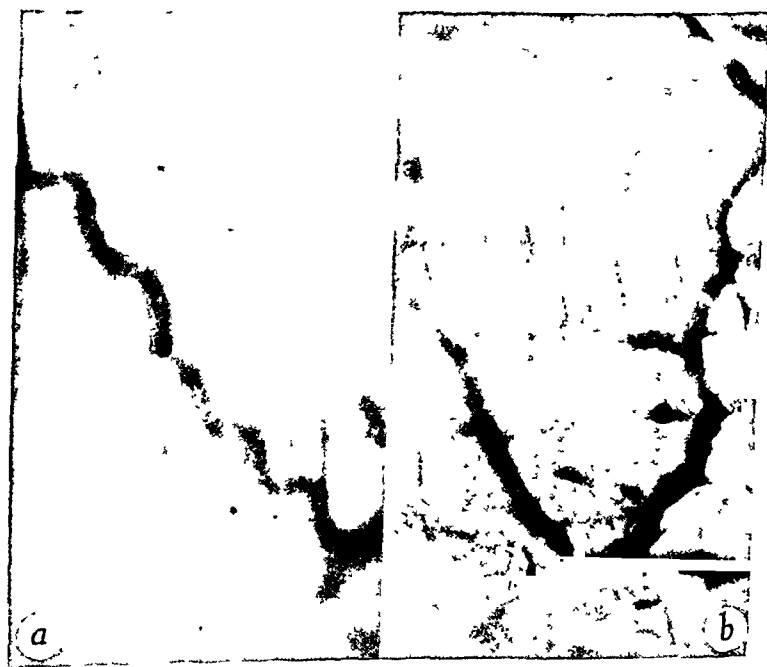


Fig. 2.—(a) Typical capillary pattern in undistended intestine, (b) same during an intraluminal distending pressure of 30 mm of mercury, ( $\times 100$ ).

Although capillary flow no longer could be seen at levels of 60 mm. or more distending intraluminal pressure, there was active circulation in the parent arteriole and venule with pressure as great as 90 mm. These vessels which continued active could be traced backward into the mesentery.

*Varying Times of Distention at a Constant Intraluminal Distending Pressure.*—At a distending pressure of 15 mm. the intestinal wall was rendered somewhat more transparent than before distention. Capillary circulation remained unchanged for periods up to five hours. Deflation was followed by reactive hyperemia of less than one-minute duration.

At a distending pressure of 30 mm. capillary flow in most cases was somewhat slower than before distention (individual corpuscles could be distinguished) but remained good (Fig. 3). This adequate capillary flow persisted for periods tested up to five hours. Flow in the larger vessels was proportionately slower. The intestinal wall was transparent. In one case in which distention was carried to five hours, flow came to an end in the capillaries at 3.5 hours but remained good in larger vessels. Deflation in all cases (including the one in which capillary flow stopped) was followed by intense dilation of all vessels and appearance of some new capillaries. In the case in which capillary flow stopped, some capillaries with stationary erythrocytes were seen thirty minutes after release of pressure. Scattered ecchymoses were also present in this case.



Fig. 3a and b—Reactive hyperemia during deflation after intraluminal distending pressure of 30 mm. of mercury ( $\times 100$ )

At higher distending pressures of 50 to 60 mm. of mercury, studied for periods of one to two hours, capillary flow was diminished in rate. This slowing of rate was soon followed by cessation of flow, which condition persisted for one to two hours. After deflation capillary flow recovered in large part. However, a few capillaries were plugged and some ecchymoses were present at the end of one hour.

*Peristalsis.*—Peristalsis was uniformly absent in the loop of intestine under study during the period of distention. It returned with vigor

following deflation. Adjacent loops, above and below the distended one, were frequently active during the period of distention in the test loop.

*Role of Kinking of Intraparietal Vessels.*—It was found that the loop of intestine studied must be long enough to prevent angulation or kinking of vessels of supply during the time of inflation. When this angulation was prevented at a distending intraluminal pressure of 30 mm. of mercury the intraparietal capillary circulation always remained good. When kinking or angulation was permitted, flow sometimes ceased in capillaries with clumping of erythrocytes and ecchymoses, even at a distending intraluminal pressure of 30 mm. Despite this, recovery of flow took place in most of these capillaries following deflation. Nevertheless, some capillaries remained plugged thirty minutes later.

*Histologic Controls.*—Sections taken from the distended test segment of intestine and control segments situated approximately 2 cm. proximal were stained and compared. At distending pressures of 15 and 30 mm. of mercury maintained for five hours there were no distinguishing histologic changes.<sup>2</sup> At higher distending pressures (50 to 60 mm.) maintained for two hours changes were seen, consisting principally of hemorrhages beneath the visceral peritoneum and into the muscular layers and mucosa. Large dilated vessels plugged with erythrocytes and disintegration of the mucosa were also noted as a result of these high distending pressures.

#### COMMENT

Landis<sup>6</sup> has pointed out that pressures in the capillaries of rat mesentery have an average value of 12.6 mm. of mercury at the venous end. At first glance one might think that an opposing distending intraluminal pressure about 13 mm. would bring capillary flow to a standstill. However, in these experiments intraluminal pressures of four to five times that value were required to bring capillary flow to an end. This may be due either to the fact that the gradient of pressure from capillary to vein<sup>7</sup> persists during intraluminal distention since such pressure probably is applied equally to intraparietal arterioles, capillaries and veins; or it may be that the intraluminal distending pressure is not entirely brought to bear on the vessels of the wall. It is possible that both these factors may operate.

A continuous flow in arterioles and venules at distending pressures of 50 to 60 mm. of mercury, although blood is no longer circulating in capillaries, may indicate the presence of arteriole-venular anastomoses, which have been described in the mesentery of the mouse<sup>8</sup> just proximal to the capillary bed or continuity of the two vessels. The improvement of flow after an initial slowing at any new distending level is similar to that which has been shown in dogs by different methods.<sup>9</sup> Deflation hyperemia also has been demonstrated by different techniques.<sup>10</sup>

Maximal intra-enteric pressure with simple experimental obstruction and in clinical cases without peristalsis is approximately 15 mm. of mercury.<sup>11</sup> Since at this value our experiments did not indicate any interference with capillary circulation for periods up to five hours, a basis is furnished for understanding the success with which obstruction of the intestine with distention is endured by the organism. Maximal intra-enteric pressure found in clinical cases with peristalsis is 23 mm.<sup>11</sup> Our series at 30 mm., representative of this group, indicated that capillary circulation usually is not obstructed by distention for as long as five hours and even though it may be, recovery of most capillaries after deflation is the rule.

In closed obstruction, higher values (50 to 60 mm. of mercury) for intraluminal distending pressures occur.<sup>12</sup> At these pressures in our experiments capillary flow ceased. However, it recovered after two hours of distention although ecchymoses and a few plugged capillaries were to be found after thirty minutes of observation following deflation.

Angulation of extraparietal vessels, ruled out in this study, must be an important additional factor in clinical cases. Observations during this study confirm this fact. Reactive hyperemia following deflation may be similar to the favorable sign surgeons seek at the operating table following deflation, indicating viability.

It is of interest that the capillaries lie at right angles to one another, to the transverse, and to the long axis of the gut. It may be suggested that their relation to circular and longitudinal muscle fibers is concerned in this pattern. The presence of two kinds of capillaries has been described already.<sup>8</sup>

#### SUMMARY

A typical pattern for intestinal intraparietal capillaries is described. Intraparietal capillary flow ceases when intraluminal distending pressure reaches 50 to 60 mm. of mercury. At an intraluminal distending pressure of 15 mm. maintained for five hours no change of intraparietal capillary circulation was detected. At an intraluminal distending pressure of 30 mm. maintained for five hours intraparietal capillary circulation was slightly slower than normal but remained adequate. At an intraluminal distending pressure of 50 to 60 mm. maintained for two hours intraparietal capillary flow ceased within one hour. Reactive hyperemia followed deflation in all series of distentions studied. If angulation or twisting of extramural vessels is permitted, intraparietal capillary flow stops at low values of distending pressure (less than 30 mm.).

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## CHRONIC PARTIAL INTESTINAL OBSTRUCTION DUE TO INTUSSUSCEPTION OF AN APPENDIX EPIPLOICA

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THE unusual pathologic picture presented at operation and the interpretation of the course of events in the clinical history prompted the report of the following case.

### CASE REPORT

P. H. (No. 486158), aged 56 years, a white, married man, noted a marked change in his usually very regular bowel habits during the twelve weeks prior to admission. This was accompanied by mild left lower quadrant abdominal discomfort; however, the constipation during this period was severe and required the constant use of cathartics. The stool was small, dry, and thin. Slight bloodstreaking of the stool was noted on a few occasions. There was free passage of flatus but no nausea or vomiting. Weight loss amounted to four pounds.

Examination revealed a well-nourished adult with two positive findings: a loop of distended bowel in the left lower quadrant, with visible peristalsis. There was no mass, tenderness, or rigidity.

*Sigmoidoscopy.*—Intestinal mucosa was normal as far as the end of the instrument.

*Röntgenography.*—Study by means of barium enemas, repeated on three occasions, revealed complete obstruction at the mid-sigmoid, with a large filling defect at that point. These findings, in the opinion of the roentgenologist, were typical of carcinoma (Fig. 1).

*Diagnosis.*—Chronic partial intestinal obstruction due to carcinoma was the pre-operative diagnosis. Polypoid tumors (polyp, submucous lipoma, etc.), or specific granulomas (actinomycosis, gumma, tuberculoma, lymphogranuloma inguinale) might cause the picture presented by this patient but such diagnoses were not seriously entertained.

*Operation.*—The abdomen was entered through a left lower rectus muscle-splitting incision. Exploration revealed a puckering of the posteromedial wall of the sigmoid with what, at first, was thought to be a submucous lipoma about 3 cm. in diameter, almost completely obstructing the lumen of the bowel. The proximal colon was dilated; the distal colon was normal. No lymph nodes were palpable in the mesosigmoid. The liver was normal; several stones were present in the gall bladder.

Closer inspection proved the lesion to be an invagination, or, better, an intussusception of an epiploic appendage into the bowel causing an almost complete obstruction (Fig. 2). Palpation through the wall of the bowel indicated to the surgeon that the mucosa was ulcerated (Fig. 3). There was no proof that the mucosal lesion was benign; it was decided, therefore, to excise the segment of bowel bearing the lesion. Accordingly, an obstructive resection was performed.

The postoperative course was uneventful. The spur was crushed on the thirteenth postoperative day; the colostomy was closed on the thirty-second postoperative day, and the patient was discharged on the sixtieth postoperative day.

*Pathology.*—Gross: Specimen consisted of a resected portion of the sigmoid which measured 10 cm. in length. The serosal surface was smooth. In the center of the specimen in the region between the anterior and lateral taenia coli there



was a puckered mass which had carried along with it an epiploic appendage. On section the part which had become invaginated consisted of a partially necrotic mass which was roughly spherical in shape and measured 3.5 cm. in diameter. The mucosal surface was greenish and necrotic at the head of the mass but at the base



Fig 1.—X-ray of barium enema, showing filling defect and obstruction at the mid-sigmoid (Oblique view.)



Fig 2.—Appendix epiploica jutting out of the "burrow" created for it by the bowel wall

the mucous membrane was granular and moderately inflamed. This mass had apparently become intussuscepted into the colon. The remainder of the mucous membrane showed no gross abnormalities. The distance between the tumor mass and

one line of resection was 3 cm., between the tumor mass and the opposite line of resection, 4.5 cm.

*Microscopic.*—On section the mass consisted of fat tissue which was connected with epiploic appendage and its surface was covered by thinned out muscle layer of intestinal wall.

*Analysis of Pathology.*—As can be seen (Fig. 2) the epiploic appendage had become intussuscepted into the sigmoid, completely surrounded by the bowel wall. This wall of the invaginated sac was composed of the normal number of layers, but the muscularis was markedly thinned (Fig. 4). The overlying mucosal surface had a chronically ulcerated base as well as acute ulceration (Fig. 3).



Fig. 2.—Bowel opened to expose mucosa. Mucosal ulceration may be seen at lower center of photograph.



Fig. 4.—Hemisection of bowel wall and epiploic appendage (gross). The bowel wall is intact although the muscle layer is markedly thinned out over the apex of the invaginated appendage.

No similar case could be found reported in the literature. The surgical importance of the appendices epiploicae has been the subject of relatively few dissertations. Littré, in 1703, is believed to have recorded

the first case with a discussion of these fatty appendages, when he found a pea-sized, white, stonelike foreign body in the abdomen of a cadaver, a free appendix epiploica.<sup>2</sup> In 1917, Harrigan<sup>3</sup> reviewed the literature to that time; since then, several reviews have appeared namely, Hunt (1919),<sup>4</sup> Klingenstein (1924),<sup>5</sup> Patterson (1933),<sup>6</sup> and Moore (1940).<sup>7</sup> Patterson<sup>6</sup> divided the diseases affecting the appendices epiploicae into four categories: inflammatory changes, torsion of the pedicle, calcification and formation of loose bodies, and incarceration in a hernial sac with or without torsion. Moore<sup>7</sup> subclassified certain of these groups, but, in all, the only mention made of intestinal obstruction, which in any way concerned the appendages, has been in connection with inflammatory adhesive bands either between appendages or from one to another organ or the parietes. A total of ten such cases<sup>8</sup> has been collected. However, no report of invagination of an appendage into the bowel could be discovered in the literature.

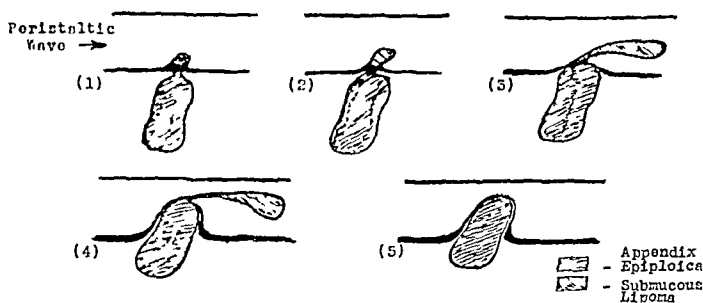


Fig. 5.—Schema of suggested pathogenesis of lesion.

It is of interest to speculate upon the etiology of this unusual picture. A congenital weakness may always be offered as a possibility, although there is no proof of it; no similar example has been previously reported. To account for the invagination one must postulate a series of unknown pressure factors within the abdomen since the intraluminal pressure due to repeated passage of firm, semisolid feces forced along by peristalsis would more likely cause an outpouching. Such an outpouching may more properly be called a diverticulum, a true diverticulum, since all the bowel coats would be involved. It may be recalled that congenital weakness is mentioned as one of the possible etiologic factors underlying the formation of diverticula (Beer,<sup>9</sup> Telling,<sup>10</sup> McGrath,<sup>11</sup> quoted by Wilkinson<sup>12</sup>).

A second and more generally accepted theory than the one mentioned above for the origin of colonic diverticula postulates that they tend to form at the base of an epiploic appendage, pushing out along a potential weakness created by the exitus of the blood vessels through the muscle coat of the bowel (Graser,<sup>13</sup> Wilkinson,<sup>12</sup> Patterson,<sup>14</sup> Grado<sup>15</sup>; and Bland-Sutton<sup>16</sup> quoted by Telling<sup>10</sup> and Hunt<sup>4</sup>). The sigmoid is probably the most common of all parts of the colon for diverticula to occur

(Wilkinson,<sup>12</sup> Spriggs and Marxer,<sup>17</sup> and MacCallum<sup>18</sup>). Their size may vary from that of a pea to the dimension of a hen's egg (McGrath<sup>11</sup>). However, its invagination cannot be easily explained. On the contrary, there usually occurs a narrowing of the neck of these out-pouchings which would tend to prevent the invagination that occurred in the case reported. The accepted theory concerning the formation of colonic diverticula and the generally known complications associated with their presence are sufficient reasons for considering an invaginated diverticulum in our case as an untenable explanation.

A plausible pathogenesis has been offered by Dr. S. Otani, Associate Pathologist to the Mt. Sinai Hospital. He suggests that a submucous lipoma (or polyp) may originally have been present, attached to the bowel wall at the site of the ulcerated mucosa covering the invaginated portion. The dragging action of the fecal stream upon this growth gradually increased its length and narrowed the neck of the pedicle, at the same time tending to invaginate the bowel wall at its base. This could weaken the muscle layer of the wall at the area subjacent to the base of an epiploic appendage and, thus, invaginate the appendage. Continued pull of the fecal stream could pull off the polypoid growth, leaving an ulcerated mucosal base which persisted (Fig. 5).

Manheim and Peskin<sup>19</sup> recently reported a case in which a submucous lipoma of the sigmoid was extruded spontaneously; in addition, they collected twenty similar cases from the literature. They state, "One theory offered is that invagination of the affected area of the intestine results in necrosis with sequestration of the intussuscepted portion." This theory would confirm Dr. Otani's theory if it could be assumed that the intussuscepted portion was not sequestered. However, we have no proof that this polypoid growth ever was present, but mention this interesting and hypothetic possibility.

*Summary.*—There is presented herewith the case history of a patient suffering from chronic partial intestinal obstruction caused by the intussusception of an epiploic appendix into the sigmoid, which, clinically, was indistinguishable from an obstructing neoplasm. The possible causes of this unusual condition are discussed.

#### APPENDUM

Since this report was accepted for publication, three additional cases of intestinal obstruction caused by epiploic appendages were reported by Giffin, H. M., Manamy, E. P., and Waugh, J. M.: *Arch. Surg.* 45: 351, 1912.

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## THE MICROSCOPIC DIAGNOSIS OF RADIOPAQUE SUBSTANCE IN THE VERMIFORM APPENDIX

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IN 1937, the curiosity of one of us was aroused by a peculiar content, I noted through the microscope, in the lumen of an appendix which had been sectioned following removal at operation. The content was interpreted as radiopaque substance, received by the patient at some time for roentgen examination. Subsequent clinical, radiographic, and pathologic study confirmed such interpretation. The content was apparently barium sulfate. Gross<sup>1</sup> and spectrophotometric<sup>2</sup> detection of barium sulfate in the extirpated appendix has been recorded in the literature. Reference, however, to observation and study identical with ours does not appear in the *Quarterly Cumulative Index Medicus* of the past twenty-five years. For this reason, as well as for the implications which it carries for pathologist, roentgenologist, and surgeon, the microscopic diagnosis of radiopaque substances, particularly barium sulfate, in the appendix is here described.

### REPORT OF CASES

From Oct. 1, 1940, to Sept. 30, 1941, 854 appendices were examined histologically at the Buffalo General Hospital. In the following ten specimens, what appeared to be barium sulfate was found microscopically.

CASE 1.—F. M., was a girl, 21 years old. The preoperative diagnosis was chronic appendicitis. Nov. 7, 1940, gastrointestinal series and barium enema were given. The appendix was visualized and Nov. 14, 1940, appendectomy was done.

CASE 2.—M. N. was a 15-year-old girl. The preoperative diagnosis was ruptured corpus luteum or chronic appendicitis. Dec. 2, 1940, gastrointestinal series was made. The appendix was visualized in a retrocecal position; it was fixed by external adhesions, tender. Dec. 4, 1940, appendectomy was done; appendix retrocecal.

CASE 3.—J. L., was a male, 21 years old. The preoperative diagnosis was appendicular colic. Nov. 29, 1940, gastrointestinal series was made. The appendix was faintly visualized, and found incompletely filled as a result of fecaliths, tender. On Dec. 2, 1940, appendectomy was done. The appendix was dilated by fecaliths.

CASE 4.—L. C. was a 43-year-old woman. The preoperative diagnosis was gastric ulcer, uterine fibroids, and chronic appendicitis. On Dec. 9, 1940, roentgen examination of the stomach and duodenum was made and gastric ulcer and duodenal diverticulum were found. On Dec. 10, 1940, resection of ulcer, hysterectomy, left salpingo-oophorectomy, and appendectomy were done. The appendix contained fecalith; chronic appendicitis.

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CASE 5.—L. D., was a woman, 10 years old. The preoperative diagnosis was fibroid uterus. On Feb 25 to 28, 1941, gastrointestinal series and barium enema were given. Esophageal diverticulum was found. The appendix was visualized. On March 8, 1941, hysterectomy, left salpingo oophorectomy, and appendectomy were done. The appendix was adherent, lumen obliterated in the distal part, and chronic periappendicitis.

CASE 6.—R. S., was a 57 year old man. The preoperative diagnosis was peptic ulcer with perforation. March 4, 1941, gastrointestinal series was started but stopped because the patient developed pain. March 11, 1941, his appendix was obtained at autopsy.

CASE 7.—N. M. was a woman, 49 years old. The preoperative diagnosis was appendical abscess with sinus. On May 7, 1941, gastrointestinal series and barium enema were given. The appendix was visualized. May 16, 1941, appendectomy was performed; histologically chronic, active appendicitis.

CASE 8.—M. C. was a 47-year old man. The preoperative diagnosis was chronic appendicitis. June 10, 1941, gastrointestinal series and barium enema were given. The appendix was visualized and on June 13, 1941, appendectomy was done.

CASE 9.—H. K. was a woman, 59 years old. The preoperative diagnosis was chronic appendicitis. On July 23, 1941, gastrointestinal series and barium enema were given. The appendix was visualized and diverticulosis of the colon was found. July 31, 1941 appendectomy was performed and the appendix was found retrocecal, adherent, and dilated by fecaliths.

CASE 10.—J. S., a male, was 27 years old. The preoperative diagnosis was interval appendicitis. On Sept 14, 1941, barium enema was given; the appendix was not visualized. Fluoroscopic examination was made of the stomach. Sept. 18, 1941, appendectomy was done and the appendix was found retrocecal, containing concretions.

From Oct 1, 1940, to Sept. 30, 1941, there were 141 appendices examined histologically at the Buffalo Childrens Hospital. In the following four specimens what appeared to be barium sulfate was found microscopically.

CASE 1.—M. H., was a female, 10 months old. The preoperative diagnosis was intussusception. On Oct 17, 1940, a barium enema was given. There was a filling defect of the cecal and ascending colon due to intussusception. On Oct 18, 1940, there was a reduction of intussusception and appendectomy was done.

CASE 2.—B. D. was a 2 year old girl. The preoperative diagnosis was intussusception. On March 11, 1941, a barium enema was given. There was cupping, and a filling defect in the midtransverse colon which receded to the cecum under force of solution. On March 11, 1941 there was a reduction of intussusception and removal of mesenteric lymph node; appendectomy was done.

CASE 3.—F. G. was a girl, 9 years old. The preoperative diagnosis was congenital intestinal obstruction. On Dec 29, 1936, gastrointestinal series and barium enema were given. March 24, 1941, gastrointestinal series and barium enema were repeated, the appendix not visualized. On April 28, 1941, gastrointestinal series was given, appendix was not visualized. On May 3, 1941, anterior gastroenterostomy and appendectomy were done. The appendix dilated, contained fecaliths.

CASE 4.—T. I. was a 6 year old boy. The preoperative diagnosis was intussusception. On Sept 1, 1941, a barium enema was given. There was a deformity of the cecum. Sept 2, 1941, after release of adhesions, appendectomy was done. In the appendix, oxyuriasis was found.

From September, 1939 to October, 1940, there were 400 appendicees examined histologically at the Niagara Falls Memorial Hospital. In the following three specimens, what appeared to be barium sulfate was found microscopically.

CASE 1.—C. P. was a man, 38 years old. The preoperative diagnosis was chronic appendicitis. On April 1, 1941, a gastrointestinal series was taken. The appendix was visualized and found to be tender. May 14, 1940, appendectomy was done; the appendix contained fecalith.

CASE 2.—R. D. was a 39-year-old man. The preoperative diagnosis was chronic peptic ulcer. On Sept. 3, 1941, a gastrointestinal series was given. When the appendix was visualized, it was discovered to be somewhat enlarged at its tip and slightly tender. Sept. 9, 1940, resection of the stomach was done for ulcer and appendectomy. The appendix contained fecalith.

CASE 3.—R. E. H. was a 9-year-old boy. The preoperative diagnosis was chronic appendicitis. Sept. 12, 1940, a gastrointestinal series was given. The appendix was visualized; retrocecal, behind midascending colon. Sept. 16, 1940, appendectomy was done; the appendix dilated.

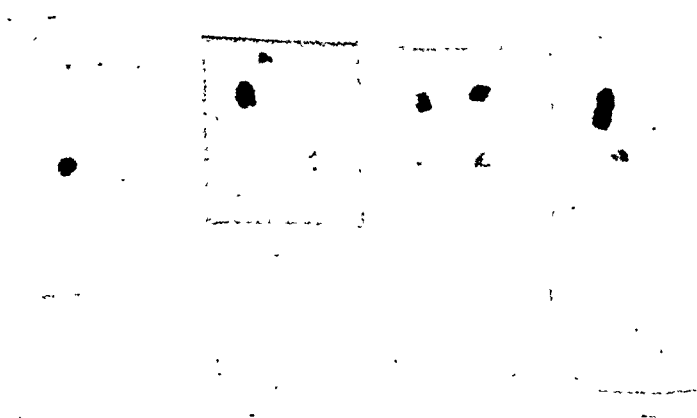


Fig. 1.—Positive prints from x-ray films of routine paraffin blocks showing, in upper row, barium in lumen of imbedded appendical segments; in lower row, control blocks with no barium in appendical lumens.

#### SUMMARY OF OBSERVATIONS

In 1,395 appendicees examined microscopically in the laboratories of the Buffalo General, Buffalo Childrens, and Niagara Falls Memorial Hospitals during one year, what appeared to be barium sulfate was discovered in the lumen of seventeen specimens.\* This discovery was made in all of the sixteen surgical cases without knowledge of history of previous radiographic examination of the patients.

Various means were employed to check our microscopic observations. In every case review of the clinical record yielded information of a gastrointestinal series or barium enema. Patients had not received oral medication which might be confused with barium sulfate. In one case

\*The incidence of the microscopic diagnosis of radiopaque substance in the appendix depends on preservation of content in the preparation of sections.



a roentgenogram of the appendix obtained at autopsy verified the content to be radiopaque substance. Similar verification was demonstrated in small segments of appendix embedded in paraffin blocks from

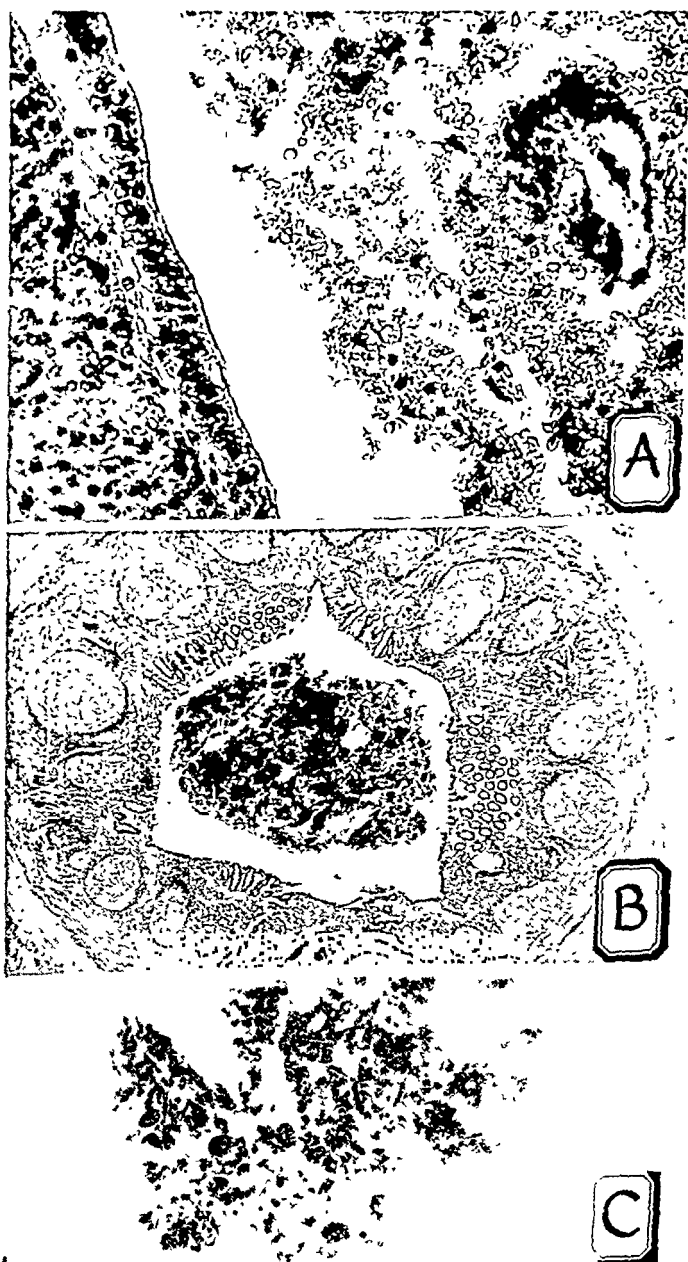


Fig. 2.—A, Barium sulfate particles in lumen of appendix (high power, strong central illumination). B, Barium sulfate particles in lumen of appendix (low power, subdued central illumination). C, Barium sulfate particles in lumen of appendix (low power, dark field illumination).

which sections had been cut, where these blocks were on hand. Density of radiopaque substance in paraffin blocks was differentiated from that of feces, fecalith with calcification, and foreign body. Roentgen study disclosed that if present in sufficient amount, radiopaque substances may be demonstrated in lumen of the appendix by x-ray films of slides made for histologic examination. Appendical content which was thought to be barium sulfate in sections of surgical specimens was compared microscopically and radiographically with the content of normal appendices filled with barium sulfate, bismuth subnitrate, and bismuth subcarbonate. From the last two drugs, the first was distinguished microscopically. Spectroscopic examination confirmed the presence of barium in three specimens, which were so tested.

When present in the lumen of the appendix in great amounts, material accepted to be barium sulfate was made out as a white, opaque substance in the gross specimen, in embedded segments, and in mounted sections. Rarely, barium sulfate in segments of appendix in paraffin blocks caused difficulty in cutting sections. With strong central illumination, barium sulfate appeared in sections on the microscope as glistening, green-gray, refractile, more or less amorphous material. With subdued central illumination it became darker in color. It was also observed as a glistening substance with dark field illumination either by use of ring stops with central disks, or of special reflecting condensers. In the polarizing microscope it presented no crystalline structure. The amount of barium sulfate in the lumen varied. It was distributed free in the lumen, mixed with feces, or incorporated in fecaliths.\*

#### COMMENT ON OBSERVATIONS

At first glance the microscopic recognition of barium sulfate in the appendix might appear to serve merely as a diagnostic trick for the pathologist. By such recognition he is enabled to startle the surgeon with the report that the patient had been subjected to radiographic examination of the gastrointestinal tract before operation.

Further thought, however, on implications of the microscopic diagnosis of barium sulfate in the extirpated appendix raises a few points of practical significance.

Concerning the interpretation of certain signs in radiographic study of the appendix, there has been a difference of opinion.<sup>2</sup> For example, one view<sup>3,4</sup> holds that the normal appendix should generally be visualized during a gastrointestinal examination. Absent or incomplete filling by radiopaque substance is looked upon as evidence of disease of the appendix. On the other side,<sup>5</sup> it is maintained that the "normal appendix is visualized only by the opportune coincidence of its filled condition to roentgenographic fluoroscopic examination. Nonvisualization

\*As an incidental note to this appendiceal study, we wish to mention that we have also made the microscopic diagnosis of barium sulfate in operative and post-mortem specimens of small intestine and colon.

never necessarily means an occluded and nonfillable appendix." In our study we showed the presence of barium sulfate in the lumen of one appendix which had not been visualized in routine radiographic examinations on three occasions.\* In respect to the problem of visualization and filling of the appendix, the microscopic diagnosis of barium sulfate along with roentgenograms of the extirpated and embedded appendix appears to offer a new and simple method, at least in one group of cases, to check the frequency with which barium sulfate enters the lumen of the appendix without detection by the roentgenologist.

Of interest is the microscopic diagnosis of barium sulfate in appendices which had not been visualized by barium enema for intussusception and which had been removed within twenty-four hours after ejection by the patient of the barium per rectum at the time of surgical reduction of intussusception.

Among the daily tasks of the pathologist is the examination of the appendix removed for "chronic appendicitis." Sometimes the appendix is the site of an inflammatory process which can be related to a previous acute lesion or can be classified as a recurrent or chronic lesion. More often the surgical specimen is described histologically as "not remarkable"; it shows no signs of active inflammation. The pathologist does not satisfactorily explain the clinical symptoms on inflammatory grounds. And the surgeon and roentgenologist interpret "chronic appendicitis" on a mechanical and functional basis. Wangenstein<sup>2b</sup> states, "Chronic appendicitis is essentially a loosely employed clinical designation for recurrent or persistent appendiceal obstruction." From a radiographic standpoint, Holmes' remarks, "In the so-called 'chronic appendix' where the infection has come and gone, there may be no evidence of the process other than fixation and failure to empty. An appendix which retains barium several days after the ascending colon has emptied is a potential source of trouble."

In our study we noted barium sulfate which had been retained in the appendix from two to forty-three days after ingestion or enema.

Two questions arise. In retention of barium sulfate, diagnosed microscopically, do we have a direct histopathologic sign indicative of disturbance in evacuation of the appendix? How far can this sign be correlated with the clinical and radiographic picture of "chronic appendicitis"?

We observed retention of barium sulfate in sections of appendices of 13 patients. Of these patients, 9 were operated upon for "chronic appendicitis," "interval appendicitis," or "appendicular colic." In only 1 appendix from this group of patients was there evidence of active inflammation. The other 7 appendices revealed: fecalith and dilatation, 2; retrocecal position and adhesions, 1; fecalith, retrocecal position, and adhesions, 1; retrocecal position and fecalith or dilatations, 2; "nothing

\*Also in another appendix, without radiographic visualization, not included in this study.

remarkable." 2. In 4 patients with retention of barium sulfate the appendix was excised at operation, or autopsy for peptic ulcer, 2; fibroid uterus, 1; congenital intestinal obstruction, 1. From this group, 1 appendix showed partial obliteration of lumen and chronic appendicitis and periappendicitis. The other 3 revealed: fecalith and dilatation, 2; "nothing remarkable," 1.

Of course, our study contains too few cases from which to draw definite conclusions on the meaning of retention of barium sulfate in the lumen of the appendix, especially of the specimen removed for "chronic appendicitis." There is no clinical follow-up of our patients. We can point out that retention of barium sulfate did occur in appendices which showed active inflammation, fecaliths, retrocecal position, and adhesions. Barium sulfate, however, was also retained in 3 appendices which were adjudged "not remarkable" within the scope of our diagnostic criteria. This last finding might be used to support the idea that "mere prolonged isolated filling of the appendix after the rest of the colon is free of barium cannot in itself be considered as evidence of pathologic condition." Yet, may not retention of the type under discussion still signify a disturbance of evacuation due to an impairment of motility of the appendix or "to augmentation of normal physiologic obstruction to its emptying" rather than due to obvious mechanical obstruction? On this basis, the microscopic diagnosis of barium sulfate in lumen asks for evaluation as a histopathologic sign of potential trouble in the appendix, for stasis may be a predisposing factor in appendiceal disease. It furnishes conditions favorable for development of fecaliths.

The results of our study may be considered with those reported by Wangenstein and his co-workers<sup>2</sup> on the detection of barium sulfate in the extirpated appendix. These investigators examined the content of appendices removed from patients who had previously received barium enema for roentgen examination of the colon, by the spectrophotometric method. Evidence of barium sulfate was absent in 13 specimens removed from 6 to 790 days after barium enema, in which the appendix was not visualized by x-ray examination, and in 4 appendices removed from 10 to 257 days after roentgen visualization with barium enema. In 6 patients with visualization of the appendix 8 hours to 6 days prior to appendectomy, barium was proved by the spectrophotometer. Morphologic descriptions of the appendix were not given in the reports of Wangenstein and his co-workers.

In 1932, Hogue<sup>8</sup> studied the effects of barium sulfate on tissue cultures from the chick embryo. Granules were ingested by various types of cells. In our case of chronic appendicitis with abscess and sinus, phagocytosis of granules had taken place.

We are indebted to Doctors E. C. Koenig, Ralph DeGraff, W. D. Langley, and B. R. Stephenson for roentgenographic, chemical, and spectroscopic assistance, and to Dr. K. L. Terplan for helpful criticism.

never necessarily means an occluded and nonfillable appendix." In our study we showed the presence of barium sulfate in the lumen of one appendix which had not been visualized in routine radiographic examinations on three occasions.\* In respect to the problem of visualization and filling of the appendix, the microscopic diagnosis of barium sulfate along with roentgenograms of the extirpated and embedded appendix appears to offer a new and simple method, at least in one group of cases, to check the frequency with which barium sulfate enters the lumen of the appendix without detection by the roentgenologist.

Of interest is the microscopic diagnosis of barium sulfate in appendices which had not been visualized by barium enema for intussusception and which had been removed within twenty-four hours after ejection by the patient of the barium per rectum at the time of surgical reduction of intussusception.

Among the daily tasks of the pathologist is the examination of the appendix removed for "chronic appendicitis." Sometimes the appendix is the site of an inflammatory process which can be related to a previous acute lesion or can be classified as a recurrent or chronic lesion. More often the surgical specimen is described histologically as "not remarkable"; it shows no signs of active inflammation. The pathologist does not satisfactorily explain the clinical symptoms on inflammatory grounds. And the surgeon and roentgenologist interpret "chronic appendicitis" on a mechanical and functional basis. Wangenstein<sup>2b</sup> states, "Chronic appendicitis is essentially a loosely employed clinical designation for recurrent or persistent appendical obstruction." From a radiographic standpoint, Holmes<sup>4</sup> remarks, "In the so-called 'chronic appendix' where the infection has come and gone, there may be no evidence of the process other than fixation and failure to empty. An appendix which retains barium several days after the ascending colon has emptied is a potential source of trouble."

In our study we noted barium sulfate which had been retained in the appendix from two to forty-three days after ingestion or enema.

Two questions arise. In retention of barium sulfate, diagnosed microscopically, do we have a direct histopathologic sign indicative of disturbance in evacuation of the appendix? How far can this sign be correlated with the clinical and radiographic picture of "chronic appendicitis"?

We observed retention of barium sulfate in sections of appendices of 13 patients. Of these patients, 9 were operated upon for "chronic appendicitis," "interval appendicitis," or "appendicular colic." In only 1 appendix from this group of patients was there evidence of active inflammation. The other 7 appendices revealed: fecalith and dilatation, 2; retrocecal position and adhesions, 1; fecalith, retrocecal position, and adhesions, 1; retrocecal position and fecalith or dilatations, 2; "nothing

\*Also in another appendix, without radiographic visualization, not included in this study.

## A METHOD OF RECONSTRUCTING THE SPHINCTERIC MECHANISM IN ANAL INCONTINENCE

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THE treatment of anal incontinence has received considerable attention in the past, and its surgical correction, in so far as it pertains to operative or traumatic origin, has been variously described. It is the purpose of this paper to present a new principle in anal reconstructive surgery which permits of a more favorable prognosis in those cases which have been classed as incurable or hopelessly beyond repair, and in which there are variable degrees of fecal seepage or passage of flatus.

While this condition does not compromise life, or even good health, the mental distress and the social ostracism of an individual so unfortunate as to be the victim of such a distressing condition are so disturbing that no apologies need be offered in presenting an attempt to alleviate the annoyance of such a discouraging condition.

The importance of an intact external sphincter may be more fully appreciated when it is recalled that Lockhart-Mummery stated that a person with a hopelessly cut and damaged internal anal sphincter would still have perfect control provided that the external sphincter were intact.

A new concept is here presented embodying an old principle in anal surgery, namely, that careful preliminary dilatation of the sphincters produces rest and relaxation necessary for primary healing with the minimum use of tension sutures.

The procedure consists of coaptation of the avulsed or lacerated sphincter by means of subcutaneous stay sutures, thorough, painstaking dilation and stretching, suture of the tendofascial caps, and subsequent repair of the vaginal vestibule.

### ETIOLOGY

In the typical case in which this procedure is especially suitable the continuity of the external sphincter muscle has been interrupted, either as the result of anal fistula surgery or of obstetrical complications. This technique does not propose to enter into the surgical treatment of any other types of incontinence except those which are myogenic in nature; the neurogenic types, such as those resulting from neoplasms, cord

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when the patient is given a high colonic flushing and placed on a non-residue diet. Each day thereafter the patient is given one ounce of mineral oil and, in addition, on the evening before operation the patient is given an enema and the perineum shaved. On the morning of operation the patient is given another colonic irrigation and no breakfast, and receives, in addition, morphine and atropine hypodermically, one hour before surgery.

#### OPERATIVE TECHNIQUE

The perineum is cleansed with soap and water and the rectum gently irrigated. The vagina is irrigated with water and bichloride of mercury solution, and 50 to 75 c.c. of aqueous solution of mercurochrome instilled preparatory to the routine repair of the perineum which is carried out if necessary. The entire skin of the perineum is then painted with a suitable skin antiseptic.

The operation is carried out under spinal or sacral block anesthesia, or if preferred, under gas-oxygen anesthesia. At the site of the perianal dimpling a heavy catgut suture on a curved cutting needle is passed through the skin, subcutaneous tissues, fascia, and muscle. This suture is tied securely to approximate intimately the dimpled ends of the sphincter muscle (Fig. 1). The right index finger is next introduced into the rectum and with slow, gentle, firm massaging and complete anesthesia the muscle is slowly stretched (Fig. 2). Massaging should

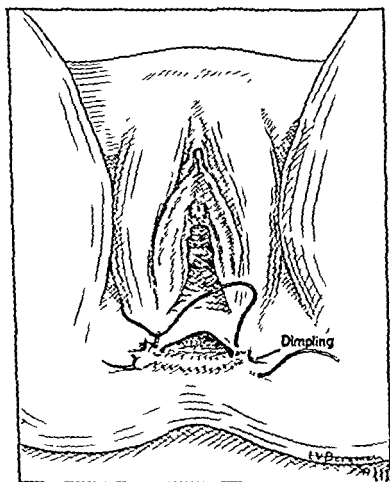


Fig. 1.

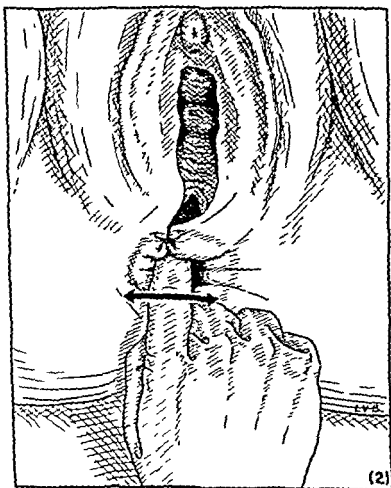


Fig. 2.

be done in a lateral manner rather than anteroposteriorly until the length of the contracted sphincter muscle measures 6 to 8 cm. This procedure should consume from twenty to thirty minutes and requires the services of at least one additional assistant. When it is felt that the muscle has been completely and thoroughly relaxed and stretched the stay suture is removed.



lesions, or cerebral hemorrhage, are not amenable to these particular maneuvers, and are not within the scope of this paper.

#### PATHOLOGY

The resulting clinical phenomena which are manifest following the division of the external sphincter assume an inglorious role as the most distressing complication in the whole field of anorectal surgery.

The pathologic picture usually presents some degree of destruction of the perineum, and varies only in that the amount of tissue presenting itself for repair following childbirth injuries is more extensive than that encountered in incontinence following anal fistula surgery.

There is usually considerable aberration of the anatomic landmarks; the thick scar tissue which eventually invests most of the circumference of the sphincter creates a cicatricial contraction and consequent retraction of the perineal area; the retracted and contracted muscle can usually be palpated along the posterior or posterolateral aspect of the anal orifice, seldom measuring more than 2 or 3 cm. in length, and the torn ends of the muscle usually terminate in fascial and connective tissue caps firmly attached to the intervening scar tissue by dense fibrous bands where dimpling of the perineal skin is often observed.

#### ANATOMY

The external anal sphincter is subcutaneous and is attached, in general, anteriorly to the perineal muscles and posteriorly to the coccyx, and is divided into a superficial and a deep lamina. The muscle fibers may extend anteriorly and posteriorly on each side of the anus inserting into the sphincter vaginae, or simply into the perineal body, or a combination of the two; or, they may also encircle the anal orifice either anteriorly or posteriorly or both, and function from a relatively fixed point, such as the coccyx or central tendon of the perineum, depending upon the completeness of the anal circumference which they encompass.

It is seen, from this, that the external sphincter does not possess a fixed anatomic pattern, but that small bundles of muscle fibers find their way by diverse routes to variable fixed points in the perineum to exert their action. The blood supply to the anterior two-thirds of the sphincter and anal outlet is derived from the perineal artery, a branch of the internal pudenda which anastomoses above with the middle hemorrhoidal artery; the posterior one-third receives its blood supply from the inferior hemorrhoidal artery. The inferior hemorrhoidal nerves follow a pattern similar to that of the vascular arbor and provide innervation through each of four sectors to include the entire circumference of the anus.

#### PREOPERATIVE PREPARATION

We feel that, as in any other surgical procedure, proper and thorough preliminary preparation is an important step in the successful management of this problem and begin our preparation about the fourth day

At the close of the operation the perianal skin subcutaneous tissues and muscles are infiltrated with nupercaine in oil (Fig. 5) as a measure of relieving any postoperative pain. Bowel movements are prevented by administering ten drops of tincture of opium three times daily for eight to ten days. The patient is placed on a nonresidue diet for ten days after which time bulkier foods are added. On the tenth postoperative day the patient is given oil retention enema and one ounce of mineral oil daily, to encourage soft-formed stools.

#### CASE REPORTS

CASE 1—This was a white woman, 30 years old. At the age of 20 years she had developed a fistula in ano which recurred after each of two operations. Sphincter control was much impaired after the second operation and completely lost after two subsequent attempts at repair. In all, twenty eight operations were performed for fistulas. The last was successful when the patient was 26 years of age. Seven different surgeons declined to attempt surgical repair because of the apparently hopeless outlook. An attempt at repair was promised on one occasion providing the patient would first submit to a colostomy. This she refused to do.

The following significant findings were revealed on physical examination: Slight rectocele, and replacement of the perineal body with thick scar tissue. Anal orifice dilatable to admit one finger. No anal sphincter except a 2 by 2.5 cm. muscle mass posteriorly. Entire anal sphincter surrounded by cicatricial tissue, except for the small area posterior to the anus.

The operation described above was carried out with an uneventful convalescence. There was normal control of defecation and gases on the eighth postoperative day. Nine months later the patient reported good control and digital examination disclosed a normally functioning anal sphincter.

CASE 2.—A white woman, 35 years of age, presented herself with a history of recurring fistula in ano of seven years' duration for which she had undergone four operations, after the second of which sphincter control was completely lost.

At 31 and 32 years of age she submitted to the last of the four procedures, without any benefit. Examination revealed a sphincter about 3 cm. in length posterior to the anal orifice. The perineum was greatly scarred, the perineal body much distorted, and a first degree rectocele presented. The outlook for clinical cure seemed hopeless. The surgical maneuvers described above were carried out and on the fourth day after operation the patient was able to expel or retain gas at will. On the twelfth day she had good control of defecation. Four years later the patient reported good control, and examination disclosed normal sphincteric function.

#### SUMMARY

A new technique is presented for reconstruction of the external anal sphincter in traumatic or operative incontinence. We feel that the procedure detailed above is of merit in properly selected cases of anal incontinence, and that it offers a definitely optimistic prognosis in many cases which were formerly classed as incurable.

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A suitable skin incision is next made over the external sphincter and the muscle exposed (Fig. 3). By careful, painstaking dissection the fascial connective-tissue caps on the ends of the muscle are isolated and left untouched. Two interrupted No. 1 chromic catgut sutures are passed through the muscle and tied (Fig. 4), approximating the two

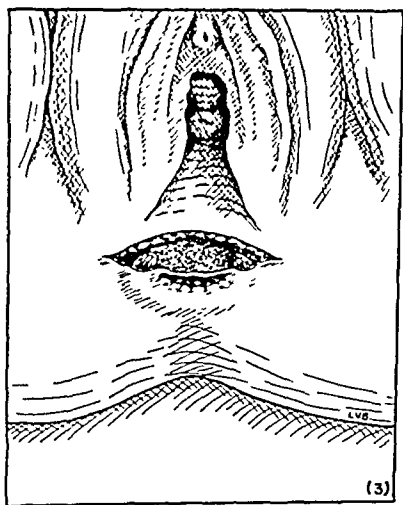


Fig. 3.

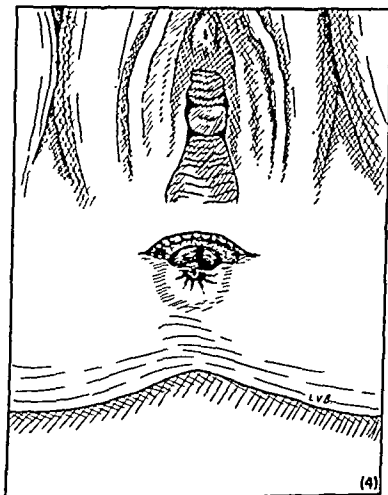


Fig. 4.

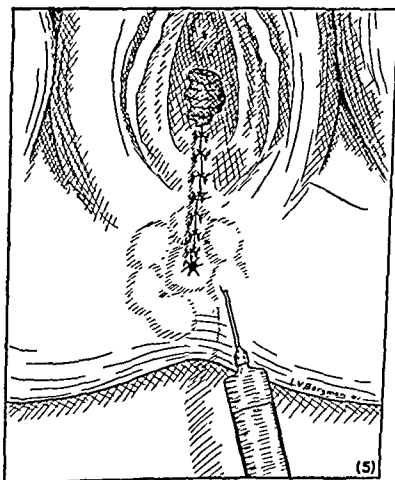


Fig. 5.

ends without strangulating the tissues involved in the suturing. The subcutaneous tissues are approximated and closed with interrupted sutures of No. 2 chromic catgut and the skin closed with black silk, silk-worm-gut, or dermal sutures. If indicated, a routing perineorrhaphy is carried out.

resected specimen. There were uninvolved lymph nodes in two appendices arising between the tumor and the one appendix containing a lymph node metastasis. This appendix was 3 cm. proximal to the tumor. The lymph node was 1 cm. lateral to the bowel wall, 2 mm. in diameter, and was completely replaced by carcinoma.

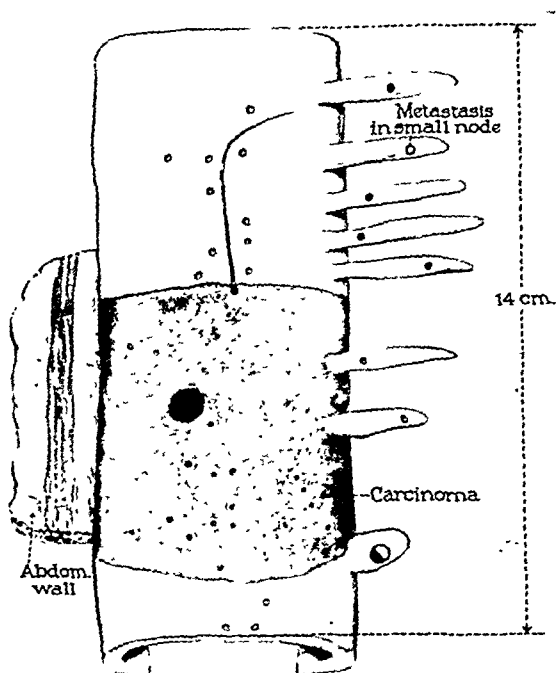


Fig. 1.—White dots over the tumor and shaded dots represent normal lymph nodes. Solid black over the tumor was a 3 mm. lymph node replaced by carcinoma. One-half of a 2 mm. lymph node in an appendix epiploica at the distal end of the tumor is replaced by a carcinoma metastasis. The lymph node 1 mm. in diameter in the fourth appendix epiploica proximal to the tumor had a small subcapsular metastasis.

The third specimen (No. 42115) was an annular carcinoma just above the peritoneal reflection. The patient was 41 years of age and had had symptoms for twenty-one months. He had developed a spontaneous fistula about 1 cm. in diameter between the carcinoma and the ileum about six inches proximal to the ileocecal valve. There were no metastases to the liver, and no peritoneal plaques. Enlarged lymph nodes were palpable to, but not above, the promontory of the sacrum. A lateral anastomosis was made around the involved ileum and a one-stage abdominoperineal resection of the rectum along with ten inches of the ileum was performed. The patient made an uneventful recovery, leaving the hospital on the twenty-second postoperative day. Ninety-two lymph nodes were microscopically sectioned in the mesentery of the rectum and seven nodes from the mesentery of the ileum. There were two appendices epiploicae in this specimen. One of these, 1.5 cm. proximal to the tumor, contained a lymph node 3 mm. in diam-

## CARCINOMA METASTASES IN APPENDICES EPIPLOICAE

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ROUVIER<sup>1</sup> in his *Anatomy of the Human Lymphatic System* does not mention the lymph drainage in the appendices epiploicae. While studying surgically removed specimens of carcinoma of the rectum and sigmoid which had been cleared by the method described by us<sup>2</sup> earlier, we were surprised to find lymph nodes often present in the appendices epiploicae. These may be from 1 to 4 mm. in diameter. In some cases they are found near the base of the appendix epiploica where it first becomes a separate stalk. More often they lie 1 to 2 cm. removed from the base, or they may be found almost at the tip of the appendix. It seems to make little difference whether the appendix epiploica is thin and slender or broad and relatively massive.

In five specimens, carcinoma metastases were present in lymph nodes found in appendices epiploicae. Fig. 1 is a drawing of one of these. This surgical specimen (No. 44112) is an annular carcinoma of the middle sigmoid removed from a man 56 years of age. It was firmly adherent to the lateral abdominal wall over an area three inches in diameter. The liver was normal. There were a number of large, palpable lymph nodes in the mesentery. The rectum and sigmoid were mobilized extensively and an obstruction resection was performed after resecting a 1 cm. layer of the abdominal wall around the adherent area. He made an uneventful recovery except for a paralytic ileus which persisted for nine days. The specimen contained forty-four lymph nodes which were sectioned microscopically. One node, 3 mm. in diameter, was found in the mesentery draining the tumor. This node was completely replaced by carcinoma. A lymph node 2 mm. in diameter was found in a small appendix epiploica just at the lower end of the tumor. This node was about 0.5 cm. from the base of the appendix and it was half replaced by carcinoma. There were eight appendices epiploicae in this specimen. The fourth appendix above the tumor had a 1 mm. lymph node which had a small subcapsular metastasis. There were three appendices between the tumor and the one containing a metastasis.

The second specimen (No. 38986) was a carcinoma completely encircling the sigmoid in a woman 27 years of age. She had had symptoms for eighteen months. An obstruction resection was performed. There were lymph node metastases to four of the sixty-seven lymph nodes sectioned. Three of these nodes were in the mesentery draining the area of the tumor. There were five appendices epiploicae in the

formed. Thirty lymph nodes were sectioned: four nodes contained metastases. In one appendix epiploica arising over the tumor, a lymph channel packed with carcinoma was found 1 cm. lateral to the base of the appendix.

In an attempt to reproduce the course of the metastases found in these specimens, injections of an India ink suspension were made into the subserosa of the antimesenteric border of the sigmoid of freshly performed autopsy specimens. With practice, less than 0.5 c.c. of the suspension can be injected and sometimes its course can be followed through the lymph channels. This injection must be made with very little pressure. The accompanying illustration (Fig. 2) shows one such preparation which was cleared as described.<sup>2</sup> At *A* the solitary lymph channel was filled with the black suspension and this passed up the antimesenteric border of the bowel in the subserosa for 2 cm. before it turned laterally and entered an appendix epiploica. The suspension filled a 1 mm. lymph node 1.5 cm. lateral to the base of the appendix epiploica. Another injection *B*, somewhat below this one, entered a single lymph channel which immediately ran into an appendix epiploica. It coursed laterally for 2.2 cm. from the base of the appendix and then made a loop and an exit from the mesenteric side of the base of the appendix and coursed down the mesentery as shown. This one preparation duplicated the manner of spread seen in our five specimens.

#### CONCLUSIONS

The injection preparations demonstrate that there are lymph channels in the subserosa on the antimesenteric border of the sigmoid which may travel at least 2 to 3 cm. lengthwise of the bowel before turning laterally to drain into the mesentery. If there are appendices epiploicae in this area, the lymph channel may drain into lymph nodes present in them, or the channels may simply traverse the appendix and drain into some of the mesenteric nodes. These injection specimens demonstrate the fact that at least 3 cm. of the sigmoid proximal to a carcinoma must be resected if a radical resection is to be performed. The finding of metastases in lymph nodes in appendices epiploicae 2 to 3 cm. removed from the primary tumor confirms this.

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eter which was completely replaced by carcinoma. The involved node was 2 cm. lateral to the bowel wall. None of the other ninety-eight lymph nodes contained metastases. The patient was still well and working twenty months after the operation.

The fourth specimen (No. 43452) was a carcinoma involving 80 per cent of the circumference of the rectosigmoid. The patient was a 47-year-old man who had had symptoms for four months. Thirty-eight lymph nodes were sectioned; ten of these contained metastases. Three appendices epiploicae arising from the bowel opposite the tumor contained lymph nodes. One of these, 1.5 cm. from the base of an appendix, contained a 2 mm. lymph node which was half replaced by carcinoma. The patient was still well twelve months after operation.

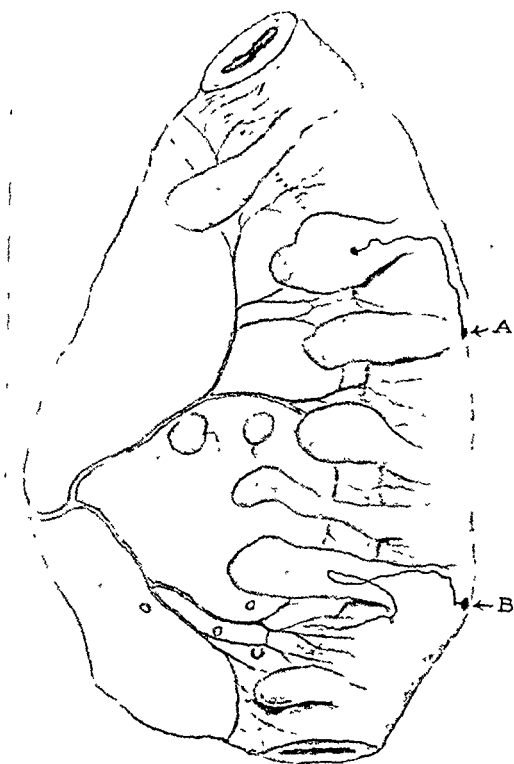


Fig. 2.—Injection of India ink suspension into antimesenteric border of human sigmoid. At A the lymph channel coursed in the submucosa for 2 cm. before turning laterally where it entered a lymph node 1.5 cm. from the base of the appendix epiploicae; it then made a loop and drained into a mesenteric node.

The fifth specimen (No. 40265) was an annular carcinoma of the sigmoid removed from a 61-year-old man who had had symptoms for three months. He had numerous metastases to the liver. There were several large distended diverticula above the tumor. Since the tumor could be removed easily, a palliative obstruction resection was per-

endothelial cells. Surrounding the reticulin fibers were massed several layers of cells of varying shapes and sizes, chiefly rounded, ovoid, and spindle shaped. These cells seemed to contain no myofibrils or acidophilic profibrils. The capillaries in general were so closely grouped that their satellite cells came into contact one with another so that the general effect was that of a mass of these cells with the capillaries scattered through them. The true relationship of cells and capillaries was only occasionally seen where there was more fibrous tissue separating them. The larger vessels in this tumor usually had fibrous walls without satellite cells and also without smooth muscle. No elastic fibers were seen with the acid orcein stain. No mitoses were identified and the growth seemed well encapsulated.

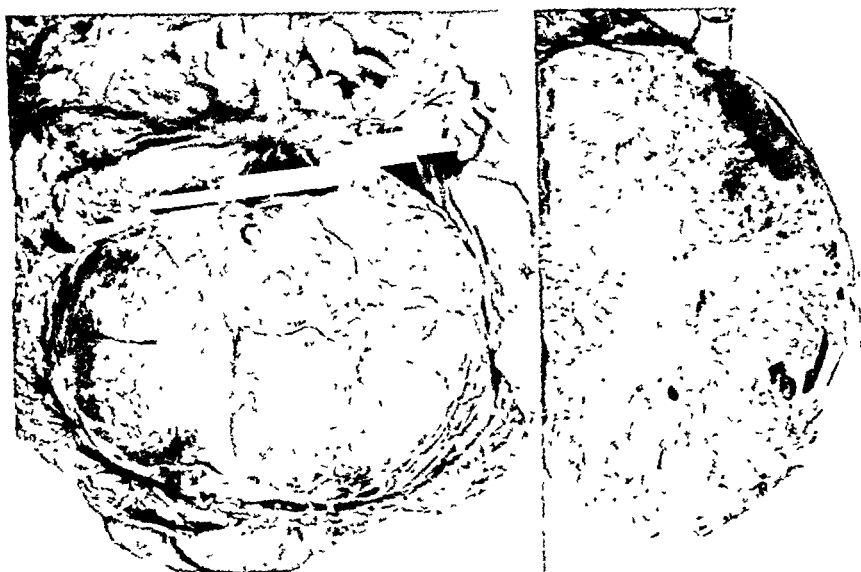


Fig 1—At the left the encapsulated tumor is shown wrapped about by omentum with large veins coursing over its surface. Above is the transverse colon. At the right is shown the cut surface of the tumor stippled with large and small blood vessels.

Since it seemed to be established that this was truly a tumor of blood vessels and not simply a highly vascular tumor of some other kind, the nature of the perivascular tumor cells came into question. It seemed incredible that they could be derived from the vascular endothelium which was everywhere of normal appearance and showed no evidence of unusual activity or morphologic change. The cells could be satisfactorily explained if we could believe that they were derived from Zimmermann's pericytes.<sup>2</sup> These are cells which are wrapped tightly about the capillaries and have contractile properties which, it is supposed, serve to narrow the caliber of the capillary lumen. Zimmermann<sup>2</sup> believed that they are modified smooth muscle cells. Recently Dr. Margaret R. Murray, by means of tissue culture, demonstrated that the epithelioid cells of the glomus tumor are pericytes.<sup>3</sup> Murray and Stout,<sup>1</sup> in reviewing a collection of 691 blood vessel tumors of all kinds found nine cases among them which in many ways resemble the present case. It was felt



## HEMANGIOPERICYTOMA OF THE OMENTUM

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THE case recorded below seems worthy of presentation because it is an example of a rare form of vascular tumor of considerable size and astonishingly long duration and freedom from symptoms occurring in the omentum where tumors of a similar nature have not been previously described. The name was recently suggested by Stout and Murray<sup>1</sup> when they reported nine tumors with similar histopathologic characteristics.

The clinical history (made available by Dr. Rineamor, Miami, Fla.) reveals that for over sixty years, the patient, S. B., white, aged 92 years, noted a mass in the right para-umbilical region. Without causing any distress or symptoms other than its mere presence, the tumor had grown very slowly and gradually, reaching its greatest size, about that of a large kidney, several years before the patient's death. The mass was firm, nontender and easily movable, seemingly not attached to any viscera. No bruit was heard over the abdomen. Although the patient was aware of the mass and had felt it for about sixty years, he never had it investigated since it was perfectly symptomless throughout the patient's life. Having had hypertension, the patient began having fibrillations a few weeks before his death. Signs and symptoms of fluid in the chest appeared, and exitus came with heart failure. The patient had no genitourinary or gastrointestinal complaints.

Post-mortem examination<sup>\*</sup> was limited to the abdominal cavity. About 100 c.c. of clear, straw-colored fluid were found in the peritoneal cavity. The kidneys were small and very firm. The tumor was found to the right of and just below the umbilicus. It was freely movable. The autopsy findings were otherwise non-contributory, being principally those of arteriosclerotic disease.

Intimately bound up within the greater omentum and adherent to the mesocolon was a large ovoid tumor measuring 12 cm. transversely, 9 cm. from above downward, and 8 cm. from before backward. It was nodular, encapsulated, and had some large veins coursing over its surface and apparently branching into the substance of the tumor. The consistence was firm, the color a mottled light gray.

The cut surface had a mottled appearance due to the presence of many minute and some larger vessels filled with blood. In the center of the tumor was a zone of fibrosis and necrosis. The necrotic portion had a faintly yellow tinge. There was no evidence of spread or infiltration, as the tumor was well circumscribed and no lymphadenopathy was present.

On microscopic examination this tumor was seen to be composed basically of tremendous numbers of small, and occasionally large, capillaries lined by endothelial cells and supported by extremely delicate reticulin fibers immediately external to the

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<sup>\*</sup>The authors are indebted to Dr. Phillip R. Rezek, pathologist of the Jackson Memorial Hospital, Miami, Fla., for permission to study the material and publish the case.

tive growth which led to the amputation of the finger before it was completely eradicated, and another metastasized to the liver and caused death. The tumor in each of these nine cases was located in the parietes, cutaneously, or subcutaneously, while in the present case the site is visceral, heretofore not reported. Its size is somewhat larger than any of the previously reported similar tumors.

#### SUMMARY

A large encapsulated vascular tumor of an unusual form has been described which apparently arose in the omentum and was palpable by the 92-year-old patient during the last sixty years of his life. The tumor was composed of capillaries surrounded by cells believed to be proliferated Zimmermann's pericytes. For this reason the name hemangiopericytoma first suggested by Stout and Murray has been used as a descriptive term.

#### REFERENCES

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3. Murray, M. R., and Stout, A. P.: The Glomus Tumor; Investigation of Its Distribution and Behavior and the Identity of Its "Epithelioid" Cell, *Am. J. Path.* 18: 183, 1942.

that they did not fulfill the criteria of glomus tumors but that the cells arranged about the vessels were probably pericytes and it was suggested that the proper name for them might be hemangiopericytoma.<sup>1</sup> This present case has strong morphologic resemblances to the majority of these nine cases and seems to belong to the same group. A majority of the tumors pursued a benign course, but one exhibited aggressive infiltra-



Fig. 2.—Low-power photomicrograph of the tumor showing the distribution of the vessels and tumor cells.

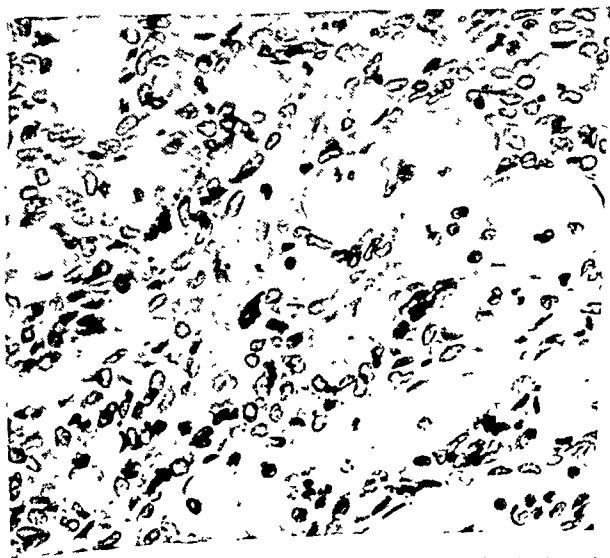


Fig. 3.—Detail showing the relationship of the tumor cells (pericytes) to the endothelial-lined capillary tubes filled with red blood cells.

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## EARLY AND LATE TOPICAL USE OF SULFATHIAZOLE IN INFECTED WOUNDS\*

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THE introduction of sulfonamide drugs directly into wounds received its impetus following Jensen and associates'¹ publication in 1939. They noted superior results following the introduction of powdered sulfonamides into débrided compound fractures and primary closure. The incidence of infection was reduced from 27.2 to 4.88 per cent.

Following the article by Jensen and his co-workers, many other workers reported their results on the local use of these drugs in clean, contaminated, or infected wounds. Most investigators have commented favorably upon its local use; others claim deleterious effects, particularly in clean wounds.

Key and Burford,² in 1940, found a high degree of protection against staphylococci infections in compound fractures following local applications of sulfanilamide. In a subsequent article³ they also advocated treating clean or potentially infected wounds. They reported 150 consecutive noninfected postoperative wounds treated by using a small amount of the drug in each wound.

Meleney⁴ points out that surgeons usually do not appreciate the number of postoperative wound infections in a series of clean hospital cases. Careful evaluation reveals an incidence of 5 to 20 per cent, varying from mild to severe infections.

Hawking⁵ found the drug diffuses quite rapidly through the wound cavity, more slowly through dead tissue, and penetrates only 2 to 3 mm. into living tissue. The basis for using sulfonamides locally is the high concentration of the drug obtainable in the immediate environment of the wound bacteria. Lockwood⁶ pointed out two additional factors influencing infection and wound healing: (1) the mobilization of cellular defense over which there is no control; and (2) the chemotherapy-inhibitor substances released by enzymatic tissue dissolution which are present in larger quantities in necrotic tissue or abscesses.

Donahue⁷ reported favorably on treating genitourinary wounds locally by dusting them with sulfanilamide. He concluded that local application reduced systemic reactions; the drug's solubility mitigated against its acting as a foreign body; and more wounds healed per primum. He cautioned that overdosage may cause tissue damage.

\*This problem was investigated before active service in the U. S. Army.

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Reports in the English literature<sup>8</sup> show a marked reduction in war wound infections following routine combined oral and topical use of sulfanilamide and sulfapyridine. Moorhead's<sup>9</sup> recent report on treating wounded soldiers and sailors who were at Pearl Harbor indicated that the administration of local sulfonamides materially reduced wound morbidity and the mortality.

Reed and Orr<sup>10</sup> recently reported their comparative results on the local use of six common sulfonamides in gas gangrene infections. Sulfathiazole was found superior to sulfanilamide and other derivatives, due to its slower absorption and greater bacteriostatic action.

In this series of experiments the local use of sulfathiazole in contaminated and infected wounds was investigated. Extraperitoneal, renal, and low abdominal wounds were contaminated with a heavy suspension of *Staphylococcus aureus*. Powdered sulfathiazole was applied locally immediately or after two to seven days. The powder was introduced by "dumping" from the bottle with a spatula and later by using an insufflator. Three groups of adult dogs were used. The operations were performed under sodium amytal intravenous anesthesia.

GROUP 1.—Eight dogs were used; no controls. A perirenal wound was infected in six dogs with a staphylococcus suspension. Sulfathiazole powder was introduced into the wound immediately in two dogs, and after two, two, four, and eight days in four dogs. In the animals given delayed treatment, the wounds were partially or completely open and suppurating. Extension of the infection was indicated by the progressive weakness of the animal, refusal to take water and food, and febrile reactions from 2 to 4° F. The reopening of these wounds for local treatment revealed deep and superficial discoloration and induration. These reopened wounds were treated with 1 to 3 Gm. of sulfathiazole. The subsequent course revealed a control of the infection and wound healing in three to six days. In two dogs each perirenal wound was contaminated and treated immediately with 1.5 and 2 Gm. of sulfathiazole. These two wounds appeared to be healed in two days, and remained closed. In the two remaining dogs of this group, low extraperitoneal abdominal wounds were infected and treated after seven days with 1 and 2 Gm. of the drug. The wounds appeared healed in four days.

GROUP 2.—Eight dogs were used, four treated and four controls. Two dogs were operated upon during the same afternoon. One perirenal wound was contaminated with staphylococci and treated immediately with 2 to 3 Gm. of sulfathiazole. The control wound was similarly contaminated, but untreated. The wounds were all closed in layers with interrupted fine silk. Three of the four treated wounds were healed in five to seven days; one was partially open the fifth day. Two of these wounds revealed slight drainage from their dependent angle. In the control group, three wounds were open and suppurating on the fifth, fifth, and seventh postoperative day (Figs. 1 A and B). One dog died on the second day, and the post-mortem studies revealed a spreading retroperitoneal infection. The febrile reactions in the untreated dogs were 1 to 2 degrees higher than in the treated series.

GROUP 3.—Nine dogs were used. In this group bilateral lower abdominal extraperitoneal wounds were utilized. The right wounds were contaminated and treated with 1 to 3 Gm. of sulfathiazole immediately or after two to three days. The left wounds were contaminated but not treated. The treated wounds revealed better healing response than the untreated. With two exceptions, the treated wounds

revealed no discharge and healed rapidly per primum. In two treated wounds there was slight drainage after two and seven days. Both of these draining wounds healed completely in ten and sixteen days. Two treated wounds revealed a fluctuant swelling without induration. Aspiration of these two wounds revealed a reddish white fluid. Determinations on these fluids for sulfathiazole concentration revealed 94.4 and 35.3 mg. per cent. In the nine control wounds there was induration, supuration, and drainage in seven. Two of the wounds, in spite of their marked induration, did not suppurate or drain.

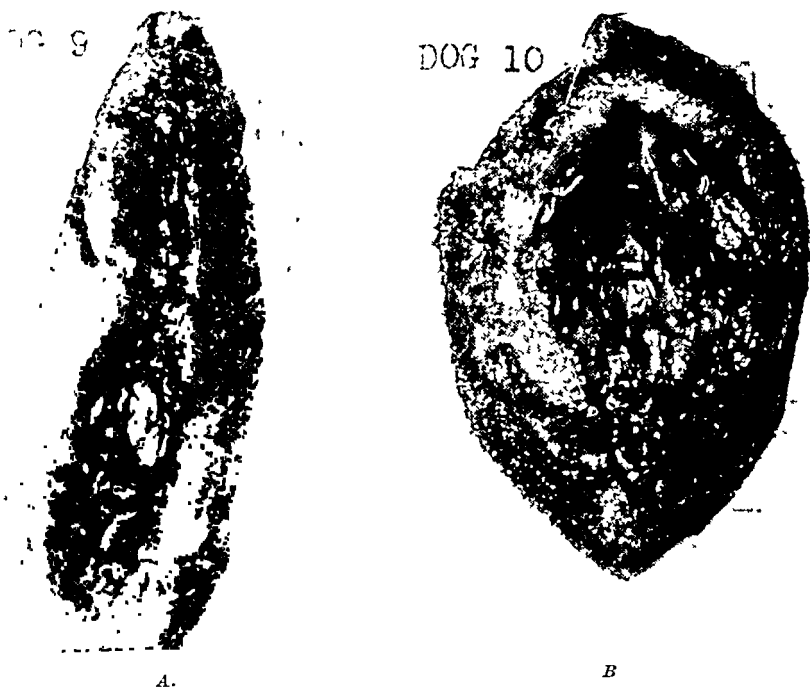


Fig. 1.—A, Partially healed perirenal wound from Group 2, Dog 9, five days after immediate treatment with 2.0 Gm. sulfathiazole had been instituted following contamination. This wound was not draining.

B, Unhealed perirenal wound from Group 2, Dog 10, five days after contamination. No sulfathiazole was applied. The wound is open widely and draining.

*Microscopic Sections* (Manshardt).—Wound closure was observed in all cases except those which were removed for microscopic study. Treated and untreated sets of wounds were removed for histologic studies from two to twenty eight days postoperatively. In general there was no striking difference in the treated or untreated wound sections (Figs. 2 and 3). In early infections, treated and untreated tissues were infiltrated with leucocytes. The vessels in the vicinity were markedly hyperemic. Tissue edema was apparent where previous induration had been noted. Foreign body response was not marked in any of the wounds. After complete healing, treated and control wounds appeared alike on microscopic sections.

#### COMMENT

Infected wounds treated locally with powdered sulfathiazole uniformly healed more rapidly and showed less reaction than did similar untreated wounds. When sulfathiazole powder was introduced im-

mediately into a contaminated wound, bacteriostasis of the *Staph. aureus* could be accomplished. When the drug was introduced into an infected wound, the extension of the infection was arrested and reparative processes were initiated. Closure of infected sulfathiazole-treated wounds was followed immediately by general improvement of the animal.



Fig. 2.—Apex of abdominal wound from Group 3 dog, seven days after immediate treatment with 2.5 Gm. sulfathiazole had been instituted following contamination. The darker staining is caused by extravasation of blood, probably traumatic.

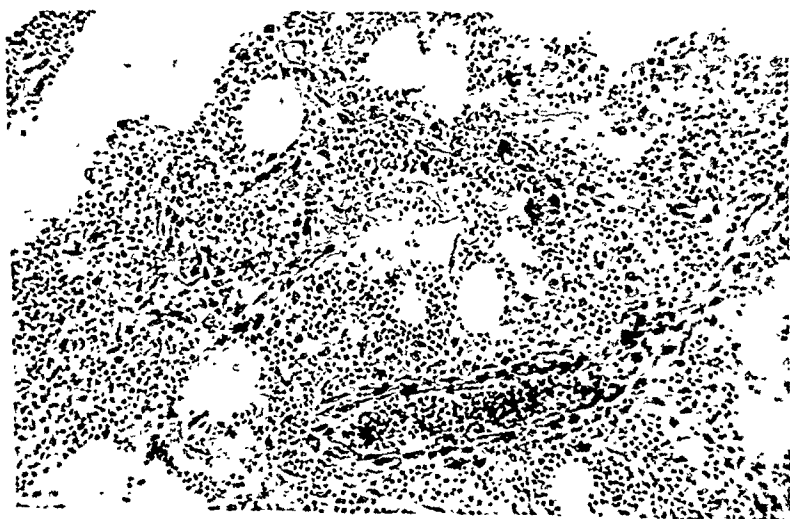


Fig. 3.—Apex of abdominal wound from Group 3 dog, seven days after contamination. No sulfathiazole was applied to this wound.

Note that both sections, Figs. 2 and 3, show apparently healthy granulation tissue. There is no significant difference in the histologic pictures.



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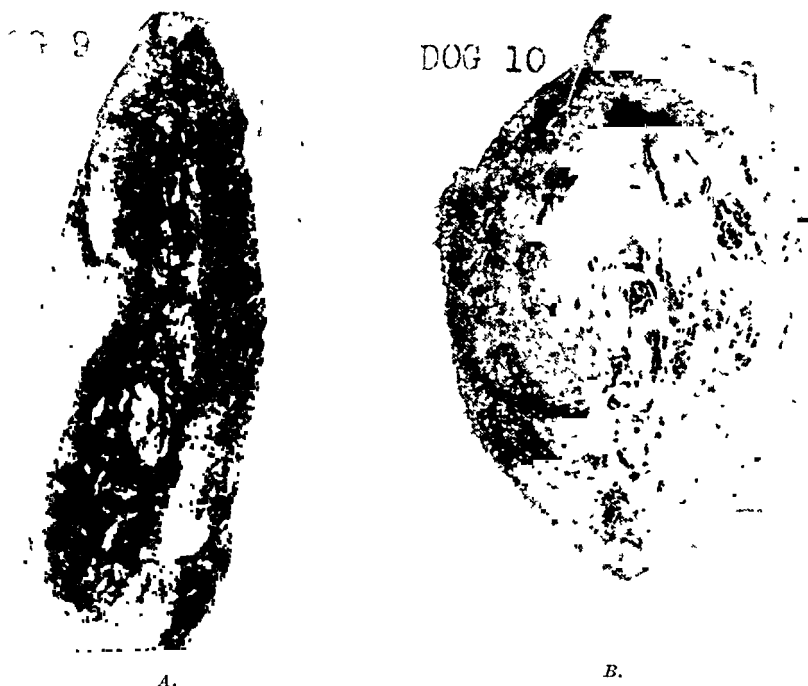


Fig. 1.—A, Partially healed perineal wound from Group 2, Dog 9, five days after immediate treatment with 20 Gm. sulfathiazole had been instituted following contamination. This wound was not draining.

B, Unhealed perineal wound from Group 2, Dog 10, five days after contamination. No sulfathiazole was applied. The wound is open widely and draining.

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The dosage of the drug should be determined by the size and the condition of the wound. Indiscriminate dumping of large amounts of the drug into a small wound may result in "caking." Acting thus as a foreign body, wound healing will be impaired and delayed. The ideal method of introducing the sulfonamide drugs in dry powder form into a wound locally is by the use of an atomizer or spray (Fig. 4). With this technique large wounds may be covered with a thin coating of the drug, including the deepest recesses. The use of moderate doses in these wounds failed to elevate the blood sulfathiazole concentration above 1 mg. per 100 c.c. of blood. Reinforced oral administration of the drug was not carried out. This is a preliminary report. Further investigations are to follow.

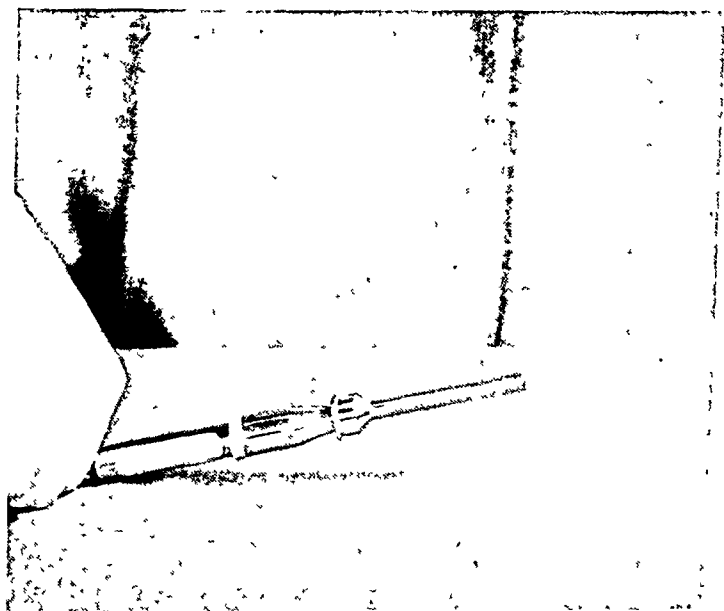


Fig. 4—This insufflator was used for topical wound treatment. The fine cloud of sulfathiazole crystals insures complete wound coverage with small amounts of the drug.

#### SUMMARY

1. Healing time and extension of infection were uniformly reduced by introducing powdered sulfathiazole locally into contaminated or infected staphylococic wounds.
2. Untoward tissue reaction to the sulfathiazole following moderate dosages was not observed in the microscopic sections
3. Sufficient drug should be introduced to cover the wound surfaces
4. The spray method is recommended to insure adequate wound distribution and to minimize the danger of overdosage and "caking" in the wound.

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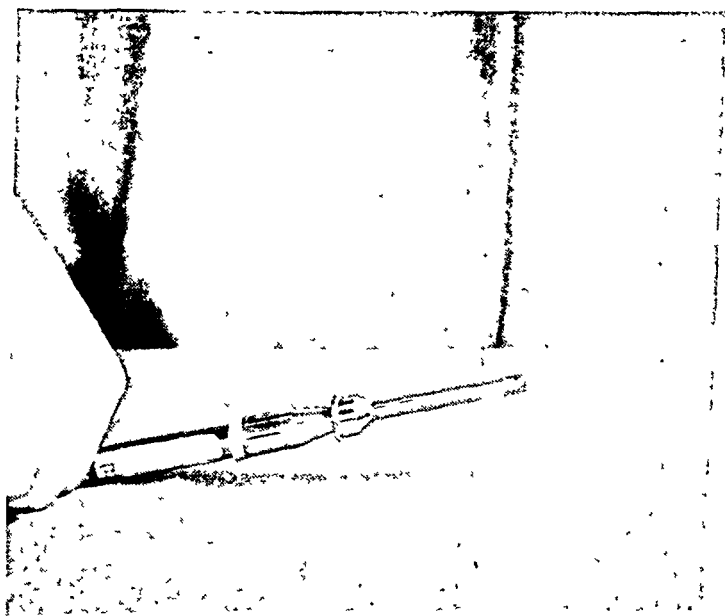


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## CHEMOTHERAPY IN PENETRATING ABDOMINAL GUNSHOT WOUNDS

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ALMOST from the time of their introduction as effective bacterial therapeutic agents, the sulfonamides have been used in the treatment of bacterial peritonitis. In February, 1937, I used prontosil and prontylin, intramuscularly and orally, successfully in a case of generalized hemolytic streptococcal peritonitis that followed the probable extraluminary rupture of an intramural abscess, resulting from an appendectomy in a girl 17 years of age. Other clinicians<sup>1,2</sup> reported recovery of patients ill with "primary" hemolytic streptococcal peritonitis, who were treated with prontosil and sulfanilamide. In 1939, Long and Bliss,<sup>3</sup> in addition to the oral and parenteral administration of sulfanilamide, suggested its use in solution through a draining sinus, into the abdominal cavity, following surgical drainage. Mueller<sup>4</sup> reported using powered "crystalline sulfanilamide directly in the peritoneal cavity at the time of operation." This was followed by an additional report with Thompson.<sup>5</sup> Jackson and Collier<sup>6</sup> reported on "experimental and clinical observations" on the use of "Sulfanilamide in the Peritoneum." Rippey<sup>7</sup> used sulfanilamide intraperitoneally in treating gunshot wounds of the abdomen. Ravdin, Rhoads, and Lockwood<sup>8</sup> found sulfanilamide therapy to influence favorably the peritonitis of appendicitis, which is usually a mixed infection. Rosenberg and Wall<sup>9</sup> placed sulfanilamide into the peritoneal cavity at the close of operations for perforated appendicitis or inflammatory disease of the pelvis. Wangenstein<sup>10</sup> reported implanting sulfanilamide about the anastomoses in certain gastric resection cases and following resections of the colon. Following the Pearl Harbor attack, Moorhead<sup>11</sup> reported a high mortality among the intra-abdominal injury cases in spite of the free use of the sulfonamides. In a later report from this same source, Ravdin and Long<sup>12</sup> stated that in the victims of abdominal injuries crystalline sulfanilamide was of great benefit to those patients who were operated upon.

### MORTALITY IN PENETRATING ABDOMINAL GUNSHOT WOUNDS

Although there appears to be a definite tendency to improve, the mortality rate in penetrating abdominal gunshot injuries is, nevertheless, still very high. The 30 per cent mortality reported by McGuire<sup>13</sup> and the 40 per cent reported by Storek,<sup>14</sup> in 35 personal cases, are

exceptional and unusual. Reports of large series, both by civilian and military surgeons, tend to indicate that the mortality rate in these victims is usually much higher. Thus, Wallace,<sup>15</sup> reporting from World War I, gives a mortality rate which averages 56.5 per cent. In a study of 112 cases,<sup>16</sup> I found a death rate of 60.7 per cent. Oberhelman and LeCount<sup>17</sup> reported 222 deaths in 343 cases or a mortality of 64.7 per cent; and Rippey<sup>18</sup> a rate of 63.4 per cent in 369 cases. Jolly,<sup>19</sup> reporting from the late Spanish Civil War, gives a mortality rate of 49.4 per cent in 243 consecutive cases. I found, in a recent study of 478 additional cases,<sup>19</sup> a fatal result in 54.8 per cent.

#### CAUSES OF DEATH

There is probably no other type of injury that presents as varied a pathologic picture at operation as is frequently found in penetrating abdominal gunshot wounds, and practically all writers, reporting studies of large series of such injuries, agree that the commonest causes of death following these injuries are (1) hemorrhage and shock and (2) general peritonitis. Other causes of death, such as pneumonia, pulmonary embolism, residual abscesses, and intestinal obstruction, occur relatively infrequently. In a previous report<sup>20</sup> I found that of 68 deaths 54.4 per cent resulted from hemorrhage and shock, 38.2 per cent from general peritonitis, and only 7.4 per cent of all fatalities were attributed to such miscellaneous causes as previously named. Hence, 92.6 per cent of all deaths in that particular group were the result of these two causes. In the 478 cases recently studied, 56.8 per cent of the patients died of hemorrhage and shock, and 40.1 per cent of general peritonitis. Oberhelman and LeCount<sup>17</sup> found, in the 205 cases autopsied, that 101, or 49.2 per cent of the patients died of hemorrhage and shock, and 95, or 46.2 per cent, of general peritonitis. Rippey<sup>21</sup> found that "shock and hemorrhage" accounted for 59.8 per cent of the deaths, and peritonitis for 29.6 per cent.

#### MANAGEMENT

The management of hemorrhage and shock in these cases no doubt ranks in importance with an intelligently planned and rapidly but carefully performed operation that is actually twofold in its purpose—first, and most important, the securing of bleeding points, and second, the repair of injuries to the hollow viscera. Because of the importance of the above facts every effort is usually made to use transfusions of blood or plasma in order to overcome the ill effects resulting from the loss of large quantities of blood. Among other measures used, the recent report of Helfrich, Cassels, and Cole,<sup>22</sup> suggests that adrenal cortical extract may be very useful in the prophylaxis and treatment of shock.

After the control of hemorrhage and shock there is the danger of a generalized peritonitis. Application of the principles advocated by



Ochsner, Gage, and Cutting,<sup>21</sup> Wangensteen and Paine,<sup>24</sup> and Bartlett<sup>22</sup> has diminished the severity of many peritoneal infections, made other patients more comfortable, and has undoubtedly improved the mortality in these cases very materially. Accordingly, the use of Fowler's position, heat to the abdomen, the maintenance of an adequate fluid and electrolyte balance, the management of ileus, and the use of continuous gastric and intestinal suction drainage have been of inestimable value in the treatment of peritonitis.

The use of chemotherapy in the treatment of this condition has been very briefly reviewed in the introduction of this presentation. The beneficial influence of the sulfonamides in the peritonitis resulting from abdominal gunshot injuries has lately aroused my interest. While engaged in the study of 478 such cases, admitted to the New Orleans Charity Hospital over a period of fifteen years prior to January 1, 1942, it was noticed that in those patients receiving some form of chemotherapy the mortality rate was lower. Accordingly, it was decided to make a separate study of all such patients and to compare them with other patients admitted during the same period of time who had not received any chemotherapy during their stay in the hospital.

#### GROUP RECEIVING CHEMOTHERAPY

The first patient in this series to be treated additionally with a sulfonamide was admitted on July 9, 1938, and died five days later of a generalized peritonitis. This patient is the first of the 9 fatal cases briefly outlined. Since this first case, and until July 9, 1942, 48 additional patients have received chemotherapy by one or more of the usual routes. In this group of 49 cases there were 9 deaths giving the almost unbelievable mortality rate of 18.4 per cent. As none of the patients in the 9 fatal cases died within twenty-four hours of admission to the hospital, it was considered unlikely that any succumbed actually to hemorrhage and shock.

#### CHEMOTHERAPY GROUP I

##### *Briefs of Fatal Cases*

HOSP. NO. 54321.—A white male, 37 years of age, had eleven perforations of the ileum with moderate hemorrhage. He was given prontosil, 20 cc, every four hours. Five days after admission, he died of general peritonitis.

HOSP. NO. 73224.—A negro male, 13 years of age, had two perforations of the stomach and moderate hemorrhage. There was evisceration nineteen days after operation and the patient died. He had been given 30 gr. sulfanilamide every three hours for three doses after operation.

HOSP. NO. 77994.—A white male, 36 years of age had no operation. He was given 10 cc. prontosil every four hours. Autopsy showed perforations of the liver, stomach, and right hemothorax. There was a massive hemorrhage. In forty eight hours, he died of "hemorrhage and shock and right hemothorax."

HOSP. NO. 51879.—The patient was a white male, 28 years old. Multiple intestinal perforations had been missed at operation. There was moderate hemorrhage. He was given sulfapyridine, 15 gr., every two hours for ten doses and neoprontosil, 5 cc. "alternately" every four hours. He died of general peritonitis.

Hosp. No. 10878.—This was a negro male, 20 years of age, with perforations of the stomach, transverse colon, and ileum. Massive hemorrhage was present. Sulfanilamide was given by mouth. There was evisceration ten days after operation. The patient died of "general peritonitis and pneumonia."

Hosp. No. 42232.—A negro male, 27 years old, had perforations of the descending colon and massive hemorrhage. He was given sulfanilamide, 0.8 per cent solution (250 c.c.) by hypodermoclysis, every six hours for six doses. He died of general peritonitis.

Hosp. No. 44254.—A negro male, 37 years of age, had perforations of the ileum, jejunum, and transverse colon. Massive hemorrhage was present. He was given sulfapyridine, 30 gr., every four hours (apparently for pneumonia). Death was attributed to "general peritonitis and pneumonia."

Hosp. No. 61059.—The patient was a negro male, 40 years old, with perforations of the stomach, jejunum, and caecum. He had massive hemorrhage and was given sulfanilamide by mouth. There was evisceration ten days after operation. He died of "general peritonitis and pneumonia."

Hosp. No. 57015.—A white male, 29 years of age, had perforation of the ileum (missed at operation) and perforation of the right femoral vein and artery (both ligated). There was massive hemorrhage. Sulfanilamide was used in the operative abdominal wall wound only. He died of general peritonitis.

#### GROUP NOT RECEIVING CHEMOTHERAPY

During the same period of time, 51 additional patients failed to receive chemotherapy in any form. In this group there were 26 deaths, resulting in a mortality rate of 50.9 per cent. A closer study of these cases shows that 11 died within twenty-four hours of admission, and in each of these the cause of death was given as "hemorrhage and shock." Exclusion of these 11 cases would show 15 deaths among 40 cases, thus giving a mortality of 37.5 per cent.

#### INFLUENCE OF SULFONAMIDES ON THE VARIOUS HEMORRHAGE GROUPS

In a previous communication<sup>20</sup> I classified hemorrhage observed in penetrating abdominal gunshot wounds into (1) slight, (2) moderate, (3) massive, and (4) unknown. The influences on the mortality rate in the various groups are given in that paper and have been recently confirmed in the 478 cases additionally studied. A study of the influence of the sulfonamides on these various groups among the 100 cases, upon which the present paper is based, revealed some interesting data, particularly in the "moderate" and the "massive" hemorrhage groups. In both those cases in which the patients were treated with the sulfonamides and those not so treated, the mortalities in the "slight" and "unknown" hemorrhage groups were the same, as not a death was recorded in either of these groups. However, a comparison of the "moderate" and "massive" groups in each instance revealed a marked difference in their respective mortality rates. In those cases in which sulfonamide therapy was used the mortality was 12 per cent and 40 per cent respectively in the "moderate" groups, while in the cases in which no sulfonamide treatment was given the comparative rates were 30.7 per cent and 91.6 per cent, respectively. Although the number of

cases in this portion of the study is relatively small the marked differences observed appear significant and probably represent a true picture of the facts involved. The loss of blood invariably results in a diminished resistance; that is, the more blood lost the more diminished is the resistance. Accordingly, those patients losing "moderate" or "massive" amounts of blood and recovering from hemorrhage and shock, frequently succumbed to the peritoneal infection. It is this particular group which is apparently greatly benefited by the use of sulfonamide therapy, especially the intraperitoneal use of sulfathiazole and sulfanilamide. A glance at Tables I and II will undoubtedly make these points clearer and even more impressive.

TABLE I  
RELATIONSHIP OF CHEMOTHERAPY TO HEMORRHAGE, IN 49 PATIENTS  
RECEIVING SULFONAMIDES\*

TYPE OF HEMORRHAGE	NUMBER	LIVED	DIED	MORTALITY RATE (PER CENT)
Slight	8	8	0	00.0
Moderate	25	22	3	12.0
Massive	15	9	6	40.0
Unknown	1	1	0	00.0
Total	49	40	9	18.4

\*In the recent group of 100 patients admitted to the New Orleans Charity Hospital from July 9, 1938, to July 9, 1942.

TABLE II  
RELATIONSHIP OF HEMORRHAGE TO MORTALITY RATE, IN 51 PATIENTS  
RECEIVING NO CHEMOTHERAPY\*

TYPE OF HEMORRHAGE	NUMBER	LIVED	DIED	MORTALITY RATE (PER CENT)
Slight	9	9	0	00.0
Moderate	13	9	4	30.7
Massive	24	2	22	91.6
Unknown	5	5	0	00.0
Total	51	25	26	50.9

\*In the recent group of 100 patients admitted to the New Orleans Charity Hospital from July 9, 1938, to July 9, 1942.

This brief study would appear to indicate that chemotherapy is of distinct benefit in the treatment of these usually serious cases, after the dangers from hemorrhage and shock have passed. The importance of this study, despite the relative paucity of cases permitting more definite conclusions, is nevertheless enhanced by the fortunate availability of a control group receiving no chemotherapy and being treated, during the same period of time, as those additionally treated with the sulfonamides. (Fig. 1.)

The sulfonamide drugs used in the 49 cases, herein considered, were given orally, intramuscularly, subcutaneously, intravenously, and intraperitoneally. Since very few surgeons handled more than one case in the entire series, there is a conspicuous lack of uniformity in the use of these drugs until the method of peritoneal implantation was started.

## INTRAPERITONEAL CHEMOTHERAPY

The recent report of Harbison and Key<sup>26</sup> in this respect seems to be of much interest. Eleven patients in the present series were treated by placing from 4 to 15 Gm. of sulfathiazole in the peritoneal cavity. Each of these 11 patients recovered, and a brief synopsis of each case is herein given. A review of the cases will show the patients to have usually suffered multiple perforations of the hollow viscera in addition to other injuries.

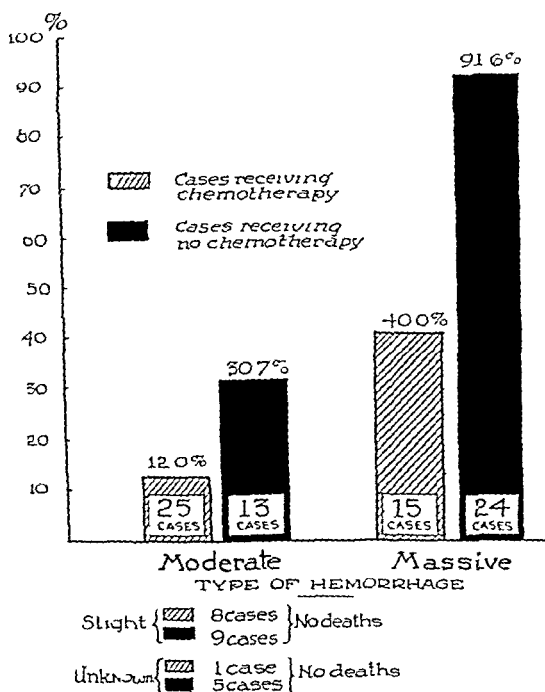


Fig. 1—Graph showing the relationship of hemorrhage to mortality rate

A lowered mortality rate in these cases, which was previously considered unlikely, now seems to be very possible. Although 49 cases is a relatively small number upon which to draw conclusions this study appears to point to a more hopeful future for victims of such injuries, especially in the group succumbing to generalized peritonitis. The 11 cases in which the patients received intraperitoneal implantation of sulfathiazole are particularly impressive since in each the peritoneum was definitely contaminated, and in some, fecal matter was removed from the cavity. It would appear from these 11 cases that the intraperitoneal use of large amounts of sulfathiazole is very effective and from all indications safe and nontoxic. However, many observers of intraperitoneal chemotherapy are of the opinion that sulfanilamide is just as effective and probably less dangerous.<sup>27-28</sup>

## CHEMOTHERAPY GROUP II

*Briefs on Cases Receiving Sulfonamide Therapy Intraperitoneally*

Hosp. No. 9528.—A negro male, 15 years of age, had eight perforations of the ileum and moderate hemorrhage. He was given 10 Gm. sulfathiazole in the peritoneal cavity and recovery followed.

Hosp. No. 12244.—The patient was a negro male, 22 years of age. He had several perforations of the stomach and slight hemorrhage. Sulfathiazole, 10 Gm. intraperitoneally, was given and recovery followed.

Hosp. No. 19340.—A negro male, 38 years old, had perforations of the stomach and small intestine. There was moderate hemorrhage. Sulfathiazole, 10 Gm. intraperitoneally, was administered, followed by recovery.

Hosp. No. 26544.—This was a negro male, 30 years of age, with numerous perforations of the ileum, jejunum, and sigmoid. He had moderate hemorrhage. Sulfathiazole was given 15 Gm. intraperitoneally. The patient recovered.

Hosp. No. 1585.—A negro male, 13 years old, had perforations of the stomach and pancreas. There was slight hemorrhage. Sulfathiazole, 10 Gm. intraperitoneally, was given, and the patient recovered.

Hosp. No. 1885.—The patient was a negro male, 24 years of age, who had perforations of the jejunum and descending colon. There was moderate hemorrhage. Sulfathiazole was given, 5 Gm. intraperitoneally, and recovery followed.

Hosp. No. 11635.—A white male, 14 years of age, had perforations of the ileum and cecum. Slight hemorrhage was present. Sulfathiazole, 10 Gm., intraperitoneally, was administered. The patient recovered.

Hosp. No. 17777.—A negro male, 23 years old, had perforations of the ileum and urinary bladder. There was moderate hemorrhage. Sulfathiazole was given 5 Gm. intraperitoneally, followed by recovery.

Hosp. No. 33771.—This was a negro male, 32 years of age. He had perforations in the transverse colon, jejunum, and left kidney. Moderate hemorrhage was present. Sulfathiazole, 5 Gm. intraperitoneally was given. The patient recovered.

Hosp. No. 45847.—A negro male, 69 years old, had perforations of the jejunum and descending colon. There was moderate hemorrhage. Sulfathiazole was given, 4 Gm. intraperitoneally, and 2½ Gm. in 500 c.c. normal saline as hypodermoclysis every eight hours. Recovery followed.

Hosp. No. 47623.—This patient was a white girl, 14 years of age. She had multiple perforations of the ileum and moderate hemorrhage. Sulfathiazole was placed about the areas of bowel perforations. A sulfanilamide-sulfadiazine mixture was used in the abdominal wall wound. Sodium sulfadiazine was given, 15 gr. intravenously, every six hours and eschatin, 2 c.c., every 2 hours. The patient was operated upon forty-one and one-half hours after being shot; she recovered.

## TOXICITY

In no case in this series in which the patient received chemotherapy was there any indication of toxicity from the drugs used. At least in none of the records was there any mention of cyanosis, nausea and vomiting, nor jaundice, certainly none that could be attributed to the use of the drugs.

## BLOOD LEVELS

No routine blood sulfonamide levels were determined in these cases. As a matter of fact, blood levels were determined in only 9 of the 49 cases. The highest recorded was 9.2 mg. per 100 c.c. of blood, observed in Case No. 17777, in which the patient received 5 Gm. of sulfathiazole intraperitoneally. Lower levels than this were the rule in nearly all

the other cases. No concentration determinations were recorded, and none were made, on the peritoneal fluid. The records additionally indicate that none of the 11 patients thus treated was surgically drained.

#### SUMMARY

The introduction of the sulfonamides, in the treatment of bacterial peritoneal infections, has added what appears to be several very effective, and apparently relatively safe, drugs to our armamentarium for the treatment of this frequently fatal disease. The implantation of these drugs, particularly sulfanilamide and sulfathiazole, into the peritoneal cavity, at the completion of a celiotomy, seems to be an especially valuable and effective way of treating generalized peritonitis.

Although hemorrhage and shock usually account for more than one-half the fatalities among victims of penetrating gunshot wounds of the abdomen, general peritonitis is not far behind, and is itself a very potent factor in the fatal cases. Only a relatively small and almost insignificant number of victims of these injuries succumb to miscellaneous causes. The recent practice of using the sulfonamides in these abdominal gunshot injuries, as apparent from the study of the cases in this presentation, has resulted in an almost unbelievable drop in the mortality rate in these victims. From all indications it is quite possible that the use of these drugs frequently helps those patients who have survived a severe hemorrhage fight off the ravages of an otherwise fatal infection. Such patients, aided with large transfusions, make unbelievably rapid recoveries.

Despite the fact that some opinions have been rather forcefully expressed regarding the dangers of the toxicity of these drugs, particularly when introduced intraperitoneally in large doses, their use in the treatment of penetrating abdominal gunshot injuries appears to be especially indicated. Although some surgeons have felt, in using the sulfonamides intraperitoneally, that the dangers of the drugs are greater than the risks of the infection, I am of the opinion that this feeling should not prevail when penetrating gunshot wounds of the abdomen, with perforations and lacerations of the hollow viscera, are considered. Certainly in the group of 49 cases herein considered there was no record of any toxic symptom attributable to these drugs.

Routine blood sulfonamide levels should be run on all cases treated with these drugs, especially when large doses are used. In cases with peritoneal drainage, a study of the peritoneal fluid concentrations, when compared with the blood levels, will at least give some idea of the rate of absorption of the drug. Among those cases in which intraperitoneal implantations of sulfathiazole were used, the amount of the drug used was no criterion to the blood level expected. Some patients receiving relatively large amounts intraperitoneally showed relatively low blood levels and vice versa.

The intraperitoneal use of the sulfonamides has appeared to obviate the need for drainage in these cases. Removal of

with suction or otherwise seems to suffice if the drug is going to be placed, in adequate dosage, into the peritoneal cavity. Additional administrations of these drugs may be by any of the several routes otherwise available to the surgeon.

#### CONCLUSIONS

1. A brief review of chemotherapy in general peritonitis is presented, showing the favorable influence of the sulfonamides upon this dreaded disease.
2. The mortality rate in penetrating abdominal gunshot wounds is still frightfully high, although a tendency to improvement appears evident.
3. About 90 per cent, and usually more, of patients with penetrating abdominal gunshot injuries succumb to (a) hemorrhage and shock, or (b) generalized peritonitis. The former cause usually predominates in large series of cases, although general peritonitis is practically invariably a very close second.
4. The management of these victims comprises the treatment of hemorrhage and shock, and, the treatment of peritonitis, which is practically always a complication when hollow viscera are injured.
5. A group of 100 cases of penetrating gunshot wounds of the abdomen admitted to the New Orleans Charity Hospital from July 9, 1938, to July 9, 1942, constitutes the material upon which this study is based. Forty-nine received some form of chemotherapy, whereas 51 were more or less similarly handled except that no sulfonamides were used as additional treatment.
6. In the chemotherapeutically treated group the mortality rate was 18.4 per cent. The 51 patients receiving no sulfonamide treatment showed a mortality of 50.9 per cent.
7. A closer study of the group treated with the sulfonamides is very impressive. The 11 patients getting intraperitoneal implantations of sulfathiazole, and showing no deaths, are especially interesting. The study leaves one with a very favorable opinion regarding chemotherapy in penetrating abdominal gunshot wounds.
8. I am of the opinion that the use of the sulfonamides, especially intraperitoneally in gunshot injuries of the intestines, will lower the mortality in these victims very materially. In the present series sulfathiazole was the only sulfonamide used intraperitoneally.
9. None of the patients treated with the sulfonamides showed any evidence of toxicity attributable to these drugs.
10. Although peritoneal fluid concentrations were not determined, none of the cases being drained, the small number of blood level determinations for these drugs failed to show any high figures in spite of large doses implanted intraperitoneally in some cases.
11. It appears that the sulfonamides are especially beneficial in those cases showing "massive" hemorrhage. Such cases showed a 91.6 per

cent mortality in the group receiving no chemotherapy as compared to the 40 per cent fatality in the group receiving additional treatment with the sulfonamides.

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## A CONSIDERATION OF EMPYEMA: ESPECIALLY ITS CHRONIC PHASE

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(*From The Clinic, Honolulu*)

CHRONIC empyema is a disease entity which fortunately is becoming less frequent due to two reasons. First, because of the remarkable results being accomplished in the treatment of pneumonias by the sulfonamides and second, because the proper treatment of acute empyema is much better understood by the medical profession at large than it was only a few years ago.

The investigations carried out by the empyema commission of the U. S. Army during World War I did more toward placing the treatment of acute empyema in this country on a rational basis than any investigations before or since. A consideration at this time of some of the more important problems connected with the proper handling of the acute empyema is pertinent to the present discussion since, theoretically at least, chronic empyema only results from improper treatment or lack of treatment of this condition in its acute phase.

An acute empyema usually becomes chronic because of one or a combination of the following factors:

1. The empyema was inadequately drained.
2. Open drainage was resorted to too early.
3. It was drained too late.
4. Underlying pathology in the lung parenchyma feeding the pleural infection.
5. The presence of bronchial fistulas.
6. The presence of foreign bodies in the pleural cavity such as pieces of drainage material, necrotic rib, etc.
7. An apparently acute pyogenic infection of the pleura may in reality be on a tuberculous, or a neoplastic basis.
8. Occasionally a subphrenic abscess may perforate through the diaphragm and give rise to a chronic infection of the pleura.

During the early part of World War I the empyemas associated with the hemolytic streptococcal pneumonias accompanying the influenza epidemics were operated upon early with an ensuing prohibitive mortality rate. The empyema commission concluded from their studies that this was largely due to subjecting these individuals to surgery too early. Deferring operation resulted in a great improvement in mortality rate, which dropped from around 40 per cent or more to 4 per cent. Graham,<sup>1</sup> who was a member of this commission, has subsequently summarized the advantages to be found by waiting until the formative stage has passed and frank pus is present, by the following:

<sup>1</sup>Received for publication, Aug. 8, 1942.

(1) There is less danger of creating a general open pneumothorax because there is a more or less circumscribed abscess shut off by adhesions from any communication with the free pleural cavity so that during the operation the pleural cavity, properly speaking, is not entered. (2) Even if an open pneumothorax is created, its harmful effects are lessened because (a) the subsidence of the active pneumonia has the effect of making the area of the air-inlet to the lungs larger than when many of the bronchioles and much of the lung parenchyma are blocked by the pneumonic process, so that the pleural opening is incapable of producing the same amount of harm; (b) the presence of adhesions and the inflammatory thickening and induration of the mediastinum tend to make it less mobile; (c) the patient's need of oxygen is less because of a more nearly normal metabolism; (d) the respiratory compensation is more efficient since, owing to a diminished toxemia, the respiratory muscles will not become so easily fatigued. (3) The patient is in better condition to withstand whatever shock there is connected with even so slight an operation as pleural drainage. (4) There is probably less risk of creating a septicemia from absorption of organisms from the fresh operation wound, an occurrence which seemed to us during the war to have happened a few times by the finding of positive blood cultures a few hours after operation in cases in which previously there had been sterile blood cultures, the operation having been done early in the disease. As a matter of fact, a patient who has recovered from his active pneumonic process, and whose mediastinum has become thickened and stiffened by adhesions so that it no longer has normal mobility, may withstand an open pneumothorax better than a normal individual.

It is conceded by everyone that if the accumulating fluid is a source of embarrassment to the cardiorespiratory mechanism, aspiration may be done without danger and occasionally, though rarely, one may be rewarded by the gratifying result of a cure by this method. Graham further states in this respect, "If, however, one uses the aspiration method to tide the patient over the pneumonic stage, the dangerous period, to be followed by open drainage later, then he is using the procedure which one of us (E. A. G.) has been advocating since 1918."

The time to discontinue aspiration in favor of open thoracotomy is largely based on the appearance and consistency of the exudate. When it becomes definitely purulent this time has arrived. Some observers advise taking the specific gravity of the aspirated exudate and believe it is time for operative interference when this reading reaches 1.040. Empyemas from pneumococcus infection may, in general, be drained with safety earlier than those resulting from streptococcus infections because the pneumonic process is of shorter duration and the exudate in the pleura becomes more rapidly purulent.

Even though the individual survives the shock of too early an operation he is still a more likely candidate for the development of a chronic empyema than he would have been with operation at the optimum time. The collapsed lung and the displaced mediastinum leave a cavity of great size to refill and the thickening of the visceral pleura and fibrous changes that take place in the lung parenchyma may prevent sufficient lung re-expansion to accomplish this end.

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<sup>1</sup>Received for publication, Aug. 8, 1912.

a primary neoplastic lesion of the lung with a secondary involvement of the pleura, though the pleural fluid when present is usually tinged with blood rather than being purulent.

In considering the treatment of an acute empyema the question arises as to the relative merits of negative suction versus other methods of handling the thoracotomy tube. In 1876, Hewett<sup>2</sup> described a very efficient means of using a closed method of drainage and since this time there has been considerable discussion of this method and various other methods and modifications. Binnie,<sup>3</sup> in speaking of the closed method of empyema drainage, made this rather apt observation, "In recent years it has been frequently rediscovered and modified in unessential details."

In my own mind, at least, I am firmly convinced that negative suction applied to the pleural cavity has very definite advantages for the following reasons:

1. Maintaining a constant intrapleural negative pressure, I believe, not only prevents the lung collapsing to the degree it would with an open thoracotomy but it would appear to be of material value in assisting in re-expansion of the lung.

2. An effort is made to place the thoracotomy tube at the most dependent area of the empyema cavity but not infrequently it is found, by digital exploration after opening into the pleura, that the opening is too high. Rather than resect a rib lower I prefer to locate the most dependent spot with my finger introduced into the pleura and then insert a mushroom catheter intercostally through a stab wound into the dependent area. This catheter is subsequently used to irrigate the cavity with Dakin's solution, saline or whatever solution is in public favor at the moment. Just now the various sulfonamides seem to have captured this coveted position. Powdered sulfanilamide, 8 Gm. dissolved in 1000 c.c. of hot sterile water, or normal saline has been recommended by Adams<sup>4</sup> and this sounds logical but with this solution I have had no experience. With negative suction to draw the irrigation fluid out of the cavity a continuous cleansing may be carried on which no doubt aids in earlier healing.

3. There is a saving in dressings and, I believe, in length of hospital stay.

One objection to suction has been that the patient is necessarily confined to bed but this objection can be obviated if the connecting tubes are left long.

In using negative suction it is important to make the tube, as it enters the chest, airtight. This can usually be done if the incision is closed snugly about the drainage tube in layers. A silk suture is passed on either side through the tube and chest wall to hold it in place. In addition the tube is brought out through a tightly fitting sterile rubber sponge. When this is strapped to the chest without any intervening dressing there is little likelihood of a leak occurring for approximately

While it is evident from the foregoing that early operation is to be avoided it is equally true, though an error less frequently committed, that late operation allows changes in the pleura and lung to take place that may contribute to the development of a chronic empyema. A large collection of purulent exudate compresses the lung and if left undrained for a long period of time causes thickening of the pleura and encasement of the lung that may prevent its subsequent re-expansion.

As has been stated, repeated aspiration may occasionally result in curing an empyema and so may intercostal drainage. Either method is not in keeping with the time-honored doctrine that pus calls for wide-open adequate drainage. We believe in resecting a generous piece of rib, enough to permit the introduction of a tube at least 2 cm. in diameter. As is well known, this should be done in the most dependent portion of the empyema cavity. The usual location, in an empyema that is not encapsulated, is the mid- or postaxillary line, resecting either the eighth or ninth rib. The pleural space normally extends lower but by the time the patient comes to operation the costophrenic angle has usually become obliterated by adhesions. It is important, also, not to place the opening too far anteriorly lest pocketing occur when the patient is recumbent.

Not only is it important to make an adequate primary opening into the pleura but it is equally important to maintain that opening until the pleural cavity has largely become obliterated and sterilized. This can be determined in the usual case by the amount and character of the exudate, though for the more fastidious, examination of smears and cultures of the exudate offers a more scientific if not a more practical determination of the time to discontinue drainage. An improperly placed and too small thoracotomy opening undoubtedly accounts for the majority of empyemas becoming chronic.

Foreign bodies such as a piece of drainage tube, a piece of necrotic rib, or other substances may account for an empyema not closing. Such foreign bodies may be picked up by x-ray, by digital exploration of the cavity, by a thoracoscopic examination, or by the use of a cystoscope in the absence of the appropriate instrument.

It is important to remember that the failure of an empyema to close may not be primarily due to the condition of the pleura but may be secondary to an involvement of the lung itself. Bronchopleural fistulas, when small, may be expected to close spontaneously but when large they tend to prevent re-expansion of the lung by interfering with increase in pressure in the bronchial tree during ordinary respiration, coughing, sneezing, straining, blowing, etc. Reinfection of the pleural cavity may occur by way of the fistula especially when it is associated with bronchiectasis, abscesses, or other types of infection of the lung parenchyma. Again one must not forget that the original lesion in the lung may have been a tuberculous one and the infection in the pleura is secondary to this plus a mixed infection. The same may be said for

chial fistula this point can be determined by the patient coughing up some of the fluid or patient detecting the presence in his nasal passages of chlorine, if Dakin's solution is used. Warning to proceed carefully in this examination is probably unnecessary.

4. Information as to size, shape, and direction of the cavity can be obtained by probing its interior with a flexible uterine sound, a method that should not be neglected.

5. Inspection of the interior of the cavity by the thoracoscope or, if this is not available, by a cystoscope may help confirm information already accumulated by the foregoing investigations. The presence of foreign bodies may be easily detected and their removal accomplished, or a specimen of pleura may be obtained for microscopic study if this seems advisable.

6. Secretion of the cavity procured from its interior as well as sputum, if any, should be studied by smear, culture, and possibly guinea pig inoculation.

7. Bronchoscopy may reveal a stricture of the bronchus proximal to its communication with the empyema cavity, and cases have been observed where dilating the stricture has aided in curing this condition.

8. If doubt exists as to the presence of bronchiectasis, especially in relation to a bronchial fistula, bronchography may be of value in determining this point and the extent of lung resection necessary in its correction.

9. General studies of the patient should be carried out to determine his cardiac reserve, vital capacity, extent of renal damage, if any, and the necessity for blood transfusions, all to be evaluated and correlated to determine his fitness for surgery.

Again in the treatment of chronic empyema all competent observers are agreed that if adequate drainage has not been established this should be done before resorting to more radical measures. Adequate drainage plus cleansing of the cavity, preferably by Dakin's solution, plus measures directed at improvement in the patient's general condition result in cure of the empyema in a majority of instances.

When these measures have been adequately tried and success has not resulted, then obliteration of the cavity by one or a combination of several methods must be resorted to. Either the chest wall must be collapsed to meet the lung, the cavity must be filled by adjacent structures usually muscle, or the lung must be freed to enable it to re-expand to meet the chest wall. Crushing the phrenic nerve on the affected side may permit the diaphragm to rise and be of material value in diminishing the size of the empyema cavity.

When the data which have just been enumerated have been collected one can proceed in an intelligent manner to deal with presenting conditions. In general, when a thorough trial has been made with adequate drainage and cavity sterilization without success, an operation

a week or ten days and during this time all the advantages of closed suction will, in all probability, have been accomplished.

There are various methods of securing negative suction. The one we have used most frequently has been by use of a water suction pump connected to the faucet, but an electrically driven suction pump is superior to this method. The least effective and the most troublesome one is by use of large bottles or demijohns connected in the same manner as a Wangensteen suction apparatus. It has the single advantage of practically always being available. An effort is made to maintain a negative suction of from 8 to 11 mm. of Hg. No ill effects from this amount of suction have been encountered.

Just when an acute empyema ceases to belong in this category and should be classified as chronic probably depends less upon the lapse of time than on the pathologic changes that have occurred in the structures surrounding the cavity. Inadequate drainage results in thickening of parietal and visceral pleura; too early drainage results in pneumothorax with collapse of the lung; while too late drainage brings about the same condition from compression of the lung by the accumulated fluid. Regardless of the reason for the lung being left collapsed, and in addition to changes in its surrounding pleura, fibrous changes take place in the lung itself which interfere with subsequent re-expansion. In general such changes have occurred at the end of three months and this is the period which is usually designated in dividing acute from chronic empyema.

When one is confronted with a case of empyema which begins to assume the aspects of becoming chronic the following investigations should be carried out to determine, if possible, the cause or causes for delayed healing.

1. If the patient from the onset has not been under one's care, a careful detailed inquiry into the history of the case may be extremely valuable, particularly so as related to the possibility of tuberculous infection.

2. Careful x-ray and fluoroscopic studies should be made to determine the size and location of the cavity, the condition of the parenchyma of the lung, the possibility of the presence of foreign bodies in the cavity, the mobility of the diaphragm, the thickness of the pleura, and the possibility of osteomyelitis of the ribs, etc.

Stereoscopic and Bucky x-ray pictures may add information, as well as views of the chest taken at different angles. Exposure following filling of the cavity with diodrast, lipiodol, or other solutions opaque to the x-rays is of special importance. The size and extent of the cavity and its relationship to surrounding structures can more easily be determined, as can the presence of pockets and the length and direction of the fistulous tract leading to the empyema cavity.

3. Filling the cavity with a measured amount of fluid will also assist in determining its size and if doubt exists as to the presence of a bron-

or with muscle flaps to fill the cavity because these measures to us seem more fraught with danger and technical difficulties and possibility of failure, while the operation as described above has given satisfactory results. If there is extensive involvement of the lung parenchyma with bronchiectasis, and/or multiple lung abscesses, the involved lobe or lobes of the lung will have to be removed before permanent cure is obtained as was the case in one of the individuals here reported.

The following case reports are presented as being illustrative of some of the points brought out in the previous discussion.

CASE 1 (No. 108,900).—P. C., a male, aged 26 years, was admitted to The Queen's Hospital Aug. 30, 1937, and discharged Nov. 25, 1937. About fourteen months previous to admission to the hospital he was operated upon elsewhere for a left empyema following pneumonia. He was in the hospital at that time for about seven months and was then discharged apparently well except for occasional purulent discharge from the thoracotomy opening. He felt well for approximately six months and then developed pain in the left chest, cough, fever, and loss of weight.

On admission to The Queen's Hospital there was a small draining sinus in the midaxillary line in the region of the ninth rib on the left side. Physical examination and x-ray studies revealed dullness and cloudiness in the left lower chest which was thought to be fluid resulting from an improperly drained empyema cavity. No evidence could be elicited in the x-ray studies suggesting pulmonary tuberculosis. His temperature was from 99 to 101 to 104° F. during the next ten days. The blood count showed hemoglobin 45 per cent, red blood cells 3,000,000, leucocytes 13,400, polymorphonuclears 77 per cent, monocytes 3, small lymphocytes 16, and large lymphocytes 4. Smears and cultures of the exudate showed Gram-positive organisms (staphylococcus) and no tubercle bacilli could be found. Urine examination was negative as was the Wassermann and Kahn. The patient was given 500 c.c. of blood on September 6, and on September 7, the hemoglobin was 60 per cent and the red blood cells 3,300,000.

*First Operation.*—Thoracotomy: On September 10, the patient was given another 500 c.c. of blood and under local anesthesia a portion of the eighth and ninth ribs in the posterior axillary line was resected, along with a piece of pleura about 1½ inches in diameter. The parietal pleura was markedly thickened, being approximately one inch in thickness. About one pint of pus was evacuated. A large rubber tube and a No 24 rubber catheter were inserted into the empyema cavity through the opening, the former for drainage, the latter to be used for irrigation. Irrigation of the cavity was done twice daily with Dakin's solution. No evidence was obtained of a bronchial fistula being present after irrigations. The patient's temperature soon came down to normal. On October 3, the tubes were removed, the chest was fluoroscoped, and the interior of the cavity explored by uterine sounds and inspected by thoracoscopy. The cavity was found to extend toward and behind the pericardium and upward to about the spine of the scapula. No evidence of a bronchial fistula could be seen and none was expected since there was no discomfort experienced by the patient following irrigation of the cavity. There were no foreign bodies visible. Though the cavity was seen to be multilocular, apparently there was no pocketing or walling off of cavities. Due to the greatly thickened parietal pleura and the absence of any appreciable diminution in size of the cavity following one month's drainage and dakinization it was decided that more radical operative interference was indicated. On September 28, the hemoglobin was 56 per cent, and red blood cells, 1,120,000. On October 6, he was given 550 c.c. of blood.



based on the Estlander-Schede principle is the procedure that gives the most satisfactory result. We proceed something as follows: an initial incision is made over the course of the rib which has previously been removed, sufficiently large after resecting the rib and cutting away a portion of the parietal pleura to explore the interior of the cavity. One is then able to extend the subsequent incision in the proper direction from the information thus obtained. Beginning at the most dependent portion of the cavity after reflecting the skin and subcutaneous tissue the entire chest wall including ribs, parietal pleura, and intercostal vessels and muscle are removed. The object is to remove sufficient of the overlying chest wall to permit the skin and subcutaneous tissue to fall in and come in contact with the visceral pleura covering the lung. During this undocking or saucerizing process search is made for pockets surrounding the main cavity and these are also undocked. If bronchial fistulas are present they are dealt with according to size, shape, and surrounding scar tissue. Small fistulas will probably close without special attention; large ones or ones held open by much surrounding scar tissue need excision and suture of the lung or excision of also a portion of the lung if bronchiectasis or abscesses are present.

The lower portion of the empyema cavity is attacked first and adequately taken care of before proceeding upward. If the cavity is at all extensive or the patient is in poor condition the operation will have to be divided into stages. The first stage is terminated by placing several rubber tissue drains or tubes up to the apex of the remaining cavity, these being brought out through the chest wall at the most dependent portion of the cavity. After partially closing the incision large dressings are applied and held in place by elastic adhesive for its compressing effect.

One or two weeks later a second attack is made through the same incision carrying it higher anteriorly and posteriorly, as the case may be, to obtain adequate exposure. The operation may be completed at this stage or subsequently, depending upon the individual case. With the incision extending up posteriorly between the scapula and the vertebral bodies the scapula can be elevated or drawn anteriorly and cavities reaching at the apex of the pleura may be dealt with without difficulty. The success of the operation depends upon adequately saucerizing the empyema cavity so that there are no overhanging edges and no pockets left undrained, thus permitting the skin and subcutaneous tissue to come into intimate contact with the visceral pleura covering the lung. The rubber tissue drains are gradually withdrawn allowing obliteration of the cavity from above downward. Continued compression during the healing process aids in obliteration of the cavity.

The removal of a large portion of the chest wall results in some deformity but not to the extent one might imagine, except in children and young individuals whose bone growth has not been completed. We have had no experience with decortication of the lung to allow its expansion

*Second Operation.*—First stage Estlander Schede procedure: The first stage was done Oct. 8, 1937, with cyclopropane anesthesia. A curved incision was made beginning posterior to the angle of the scapula and extending down anteriorly over the ninth rib to the nipple line (Fig. 1). Portions of the eighth, ninth, and tenth ribs were resected with the underlying pleura so as to saucerize completely the lower portion of the empyema cavity (Fig. 2). The upper part of the cavity lying beneath the scapula was packed with vaseline gauze and rubber tissue drains which were brought out through the lower part of the incision and the wound was partially closed. On October 11, transfusion of 550 c.c. of blood was given. October 16, hemoglobin was 65 per cent and red blood cells 4,120,000. October 21, transfusion of 500 c.c. of blood was given.

*Third Operation.*—Second stage Estlander Schede procedure. The same incision was opened and carried higher and posteriorly between the scapula and the posterior spinous processes. Portions of the fifth, sixth, and seventh ribs with underlying pleura were removed so as to complete the saucerization or undocking process over the entire empyema cavity. Drains were inserted as before and brought out through the dependent portion of the incision. The incision was partially closed. These drains were slowly removed as the operative wound healed.

*Fourth Operation.*—The last operation was done November 5. The phrenic nerve on the left was crushed above the clavicle. Following each removal of ribs and parietal pleura the wound was covered with large dressings and snugly strapped with elastoplast to aid in the caving in process of the chest wall. Microscopic examination of the pleura removed at each operation showed no evidence of tuberculosis, only scar tissue and inflammatory reaction. On November 25, or 87 days following admission to the hospital, the patient was discharged with the wound practically healed. He soon returned to his former occupation, that of barber, and has been free of symptoms since.

CASE 2.—A man, aged 49 years, was admitted to Leahi Home on Dec. 21, 1937. On Nov. 2, 1937, he had been operated upon elsewhere for acute appendicitis under general anesthesia and was discharged on Nov. 13, 1937. On Nov. 23, 1937, while resting at home he had a severe attack of chills and fever with some cough, expectoration, and night sweats, and also some pain in the left chest posteriorly. He had lost during this time sixteen pounds in weight. On examination there was dullness of the entire right upper lung anteriorly and posteriorly with bronchial breath sounds but no râles, and the left lung was clear. Wassermann and Kahn were negative. Urinalysis showed a trace of albumin. Blood count was 61 per cent hemoglobin with 4,200,000 red blood cells and a white count of 10,500. Sputum on eighteen examinations was negative for tubercle bacilli. Mantoux in the first dilution was positive. X ray showed pneumonic infiltration with cavity in the right upper lung. On Jan. 22, 1938, the patient was fluoroscoped and the right costophrenic sinus was seen to be obscured with development of early pleural effusion. This was aspirated on the following day and 50 c.c. of slightly bloody fluid were obtained, which showed on microscopic examination a 1,500 cell count, 70 per cent being polymorphonuclear cells. Culture was negative for acid-fast and other organisms. Following the pleural effusion the patient became much worse. He became extremely toxic with high septic temperature and blood count rising to 29,000 with 89 per cent polymuclear leucocytes. Another thoracentesis showed the development of a foul empyema. On Feb. 1, 1938, a portion of the tenth rib in the right posterior axillary line was removed and the empyema drained. Following this procedure and after several blood transfusions the patient's condition improved considerably. There was still expectoration of about 100 c.c. of purulent material daily and the temperature was never flat. The empyema cavity was irrigated daily but this was stopped when the patient began to expectorate fluid used for irrigating, proving the presence of bronchopleural fistula. On May 18, 1938, bronchoscopy was performed.

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*Third Operation.*—Second stage Estlander-Schede procedure. The same incision was opened and carried higher and posteriorly between the scapula and the posterior spinous processes. Portions of the fifth, sixth, and seventh ribs with underlying pleura were removed so as to complete the saucerization or underking process over the entire empyema cavity. Drains were inserted as before and brought out through the dependent portion of the incision. The incision was partially closed. These drains were slowly removed as the operative wound healed.

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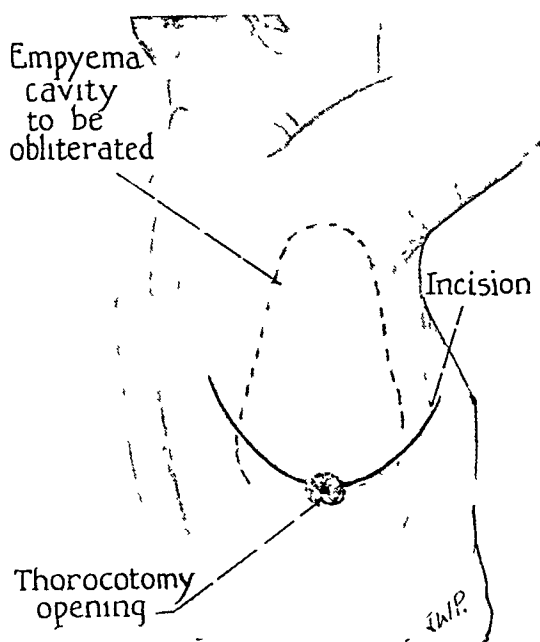


Fig 1

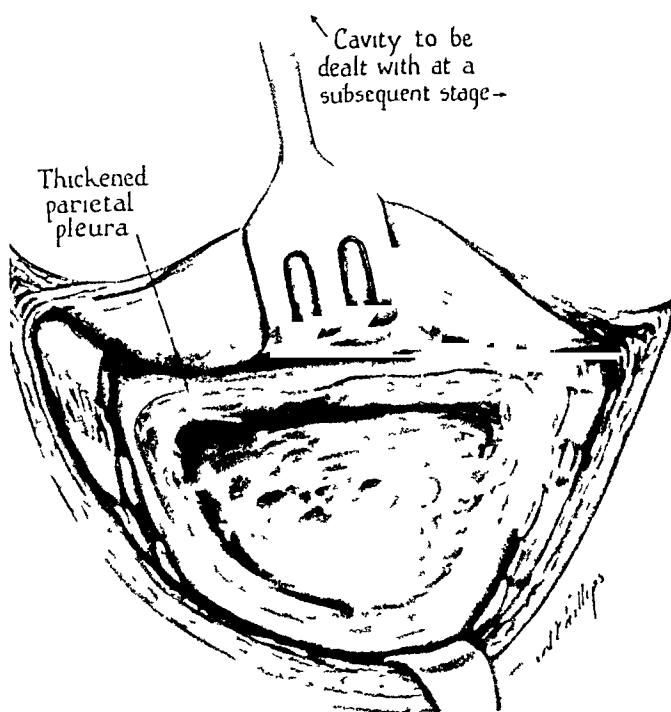


Fig 2

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*Third Operation.*—Second stage Estlander Schede procedure. The same incision was opened and carried higher and posteriorly between the scapula and the posterior spinous processes. Portions of the fifth, sixth, and seventh ribs with underlying pleura were removed so as to complete the sacralization or undocking process over the entire empyema cavity. Drains were inserted as before and brought out through the dependent portion of the incision. The incision was partially closed. These drains were slowly removed as the operative wound healed.

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The findings disclosed marked hyperemia of the entire tracheobronchial tree with pus coming from the right upper lobe bronchus but no evidence of neoplasm. Because of his intermittent high elevation of temperature and failure to improve, lipiodol was instilled into the chest wall sinus. X ray showed a sinus leading posteriorly and terminating in a large pocket. A second operation was done on June 29, 1938, at which time resection of the eighth and ninth ribs posteriorly was done and the entire empyema cavity was laid open and packed. Following this operation and another blood transfusion the patient's condition improved and his temperature dropped to normal. A right permanent phrenectomy was performed on July 16, 1938, in an attempt to obliterate the empyema cavity and the broncho-pleural fistula. Positive sputum for tuberculosis was obtained on several occasions: on Jan 10, 1938 on guinea pig inoculation, May 18, 1938, on bronchial smear taken during bronchoscopy, and one sputum culture. Microscopic section of the removed pleura revealed one typical tubercle.

At present the empyema cavity has been completely obliterated and the external incision has healed. The final conclusion was that this individual had suffered from (1) abscess of the lung on the right which ruptured into the pleura and caused his empyema, and (2) pulmonary tuberculosis with secondary involvement of the pleura.

CASE 3—A girl, aged 10 years, first came under my care on July 25, 1938. She had been operated upon three times, elsewhere, for drainage of a right empyema which presumably followed pneumonia. Examination revealed an obviously sick, debilitated child with a draining empyema cavity. X ray showed a large encapsulated empyema cavity over which extensive resections had been done of portions of the fifth, sixth, seventh, and eighth ribs. Without going into the uninteresting details of the conduct of this case, which covered a period of three years and involved fifteen additional operative procedures, the points of greatest interest and of practical value will be briefly discussed.

No evidence of tuberculosis could be found in x rays of the chest, smears and culture of the discharge, or in sections of pleura and lung subsequently excised. Examination showed bronchial fistulas brought out when the patient was asked to hold her nose and blow, and this was confirmed by irrigation with Dakin's solution and subsequently at operation. The patient's general condition was improved by transfusion, administration of vitamins, and other supportive measures.

As a first procedure more dependent drainage was instituted and while this diminished the amount of discharge, it continued. Large areas of thickened parietal pleura and ribs were resected but due to mobility of the mediastinum, the heart and other mediastinal structures moved over into the left chest and the empyema cavity persisted. The phrenic nerve was temporarily paralyzed and subsequently removed, and though this diminished the size of the cavity from below upwards it persisted and continued to pour out purulent discharge. Bronchoscopic and bronchographic examinations were done and it was concluded that bronchiectasis plus lung infection was contributing to the persistence of the empyema. The removal of the two lower lobes, or at least the portion containing the bronchial fistulas seemed advisable. Meanwhile, due to the patient's youth postural changes began to occur and the subsequent scoliosis resulted in the chest becoming very deformed. This has been greatly improved and prevented from developing further by braces. Attempt at removal of the lower lobes resulted in early onset of shock so that this had to be carried out in many stages. Each specimen of the lung tissue removed showed dilated bronchi with eroded and denuded epithelium and multiple nonsuppurative abscesses scattered about in atelectatic lung tissue.

With removal of all of the involved lung the empyema cavity has filled in and healed but the individual has been left with a much deformed thorax.

These three cases are cited in order to illustrate the usual types of chronic empyema which one may encounter. The first case was one in which the pleural cavity alone was involved, and, no doubt, had early adequate dependent and more continuous drainage been instituted, would have healed without becoming chronic. The second case probably resulted from the rupture of a lung abscess into the pleura and was complicated by pulmonary tuberculosis which, fortunately, responded to more conservative treatment than does the usual case of tuberculous empyema. The third individual represents the most serious type of nonspecific pleural infection. The empyema, no doubt, would have healed by conservative measures had it not been continuously reinfected by the underlying lung involvement.

In conclusion, I wish to emphasize the fact that there is an optimum time for operating upon infections involving the pleura and that when an adequate operation is done at this time there is little likelihood of the empyema becoming chronic.

When an empyema does become chronic the methods of procedure to determine why this has occurred are discussed and finally three representative case histories have been cited to illustrate various methods of dealing with various types of chronic empyema.

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# A NEW PROCEDURE FOR HIGH-FREQUENCY COAGULATION

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THE object of this report is to describe a method which may be used to advantage when it is necessary to produce hemostasis by coagulation, either in special or in general surgery or in experimental surgery on animals. In the usual procedure the surgeon grasps the blood vessel with a forceps, after which an assistant touches the forceps with the electrode from the high-frequency machine, the foot switch of which is operated by another assistant or nurse. With such an arrangement the surgeon lacks complete control over the manipulation, the delicacy of which must often be of a high order. Furthermore, the assistant may obscure the field of view at a time when obscurity is least desirable.

All of the above difficulties are avoided by the new procedure which entails the use of an easily detachable clip which is slipped over the upper end of the forceps that is to be used in the coagulation, the clip being connected to a wire leading from the high frequency machine. In our case the clip consists of a small piece of spring brass which was milled to take our particular forceps and bent as shown in Fig. 1. A tapered socket was made from the hilt of an old hypodermic needle and soldered into the brassclip. A tapered plug was made to fit this socket and the wire soldered to this. The wire can therefore be disconnected at any time and the forceps used in a purely surgical manner. A special clip may be designed to fit any type of forceps or clamp which it may be desired to transform into a coagulating electrode without damage to the instrument. The small radio "alligator" clip may be adapted to connect the high-frequency current to odd-shaped clamps.



Fig. 1.—Forceps and connections for high-frequency coagulation: a, forceps; b, detachable clip; c, plug which is soldered to wire (d) and inserted into socket on clip (b); d, wire leading from high frequency machine.

In order to coagulate a blood vessel, the surgeon merely grasps the vessel with the forceps and he or another person presses the foot switch. Thus, there is avoided the crossing and interference with the operative fields by a second person, as well as the danger of moving or displacing the coagulating electrode when the contact is made in the customary way. The control of the coagulation is, therefore, directly in the hands of the surgeon, and an assistant is not necessary. Furthermore, the time spent in coagulating is reduced to one-half or less, and the loss of blood is kept at a minimum.



# Editorial

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## International Society of Surgery

THE International Society of Surgery, the greatest international surgical organization in the world, has transferred its headquarters from Brussels, Belgium, to the United States. This action was taken by a vote of the delegates of all of the affiliated societies of the Americas, representing Argentina, Brazil, Canada, Cuba, Ecuador, Guatemala, Mexico, Paraguay, Peru, the United States, Uruguay, and Venezuela. Headquarters of the Society will be in the Inter-America Division of the New York Academy of Medicine in New York City.

Dr. Rudolph Matas, of New Orleans, immediate past president of the International Society of Surgery and who at the present time is acting secretary and treasurer of the Society, stated in explaining the need for the change in headquarters: "The German occupation of Belgium and the Nazi devastation of the rest of Europe and all the other war-torn, ruined nations had virtually restricted the international relations of the Society to the Western Hemisphere where its fellowship is widely spread through its affiliated branches in North, Central, and South America. The executive committee of the United States division, the largest, most active contributor to its transactions, felt it a duty conjointly with their Latin American colleagues to rescue the Society out of the perils of the European conflagration. The first steps were taken in November, 1941, at Boston, but no final action could be taken to transfer the official sanctum in Brussels to America without the concurrence and approval of all the affiliated branches in America."

The executive committee which has been chosen is as follows: Dr. Elliott C. Cutler, Colonel, Medical Corps, U. S. Army, chairman in absentia; Dr. Rudolph Matas, acting secretary and treasurer; Dr. Eugene Pool; and Dr. Arthur W. Allen. At a recent meeting of the executive committee on Nov. 12, 1942, it was decided that Dr. José Arce, dean of the University of Buenos Aires, would serve as acting president of the International Society of Surgery in the absence of Professor L. Meyer, of Brussels, detained in Belgium by Nazi compulsion. At this meeting a revision of the constitution was adopted, which had been prepared previously by Dr. Matas of New Orleans.

It is of significance, particularly at this time, that the headquarters of the International Society of Surgery will be in the Inter-American division of the New York Academy of Medicine, where Dr. Enrique Cervantes, assistant secretary and treasurer of the executive committee, who is the editor of *América Clínica*, has his offices. *América Clínica* will be the official journal of the Society, so that Dr. Cervantes will be able to give particularly valuable service not only to the North American but also to the Central and South American members of the society.

—Alton Ochsner, M.D.  
New Orleans, La.

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## AMEBIC HEPATITIS AND HEPATIC ABSCESS

AN ANALYSIS OF 181 CASES WITH REVIEW OF THE LITERATURE

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*(From the Department of Surgery, School of Medicine, Tulane University, and the Ochsner Clinic)*

*(Continued from the March issue)*

*Treatment.*—The treatment of amebic hepatic infection is entirely surgical, although it should be realized that this may consist of either conservative or radical measures, depending upon certain developmental factors. As previously stated, the obvious rationale of this principle is based upon the fact that early recognition of an amebic hepatitis and the institution of conservative measures during this presuppurative stage may prevent progression to actual abscess formation. Moreover, even in cases in which early abscess formation has occurred, conservative measures are frequently sufficient to effect complete resolution.

The term conservative therapy is used to signify the administration of the specific drug emetine hydrochloride, with or without aspiration, depending upon the presence of indications for the latter. In early cases of amebic hepatitis, utilization of emetine alone may be sufficient (Case 1). More recently Greig<sup>145-147</sup> and Sarmiento<sup>339</sup> have directed attention to the importance of this fact. In other cases, however, a true abscess has apparently developed which requires in addition to the emetine, evacuation of its contents by aspiration (Cases 2 and 3). It is for this reason that Rogers and Megaw<sup>326, 329</sup> have emphasized the importance of recognizing these hepatic complications as early as possible. These facts are clearly demonstrated by Cases 1, 2, and 3 reported in this communication.

In 1911, Vedder<sup>380, 381</sup> undoubtedly made one of the most important advances in the therapeutic consideration of amebiasis with the introduction of emetine. Perhaps of equal significance was its subsequent popularization in amebic hepatitis by Rogers.<sup>321-323</sup> Of interest in this connection is the claim by Huard and associates<sup>171</sup> that it was used by Florence<sup>125</sup> thirty years earlier. Magendie and Pelletier,<sup>229</sup> in 1817, described emetine as an alkaloid in ipecacuanha which is the dried root of *Psychotria ipecacuanha*. A decoction of this root, which was originally found in Brazil but has since been cultivated in India and other

regions, was long used by the natives in the treatment of diarrhea and dysentery. Rogers and Megaw<sup>329</sup> state that its therapeutic use was introduced in India as early as 1660 although its popular usage did not begin until about the middle of the nineteenth century. De Savignac,<sup>33</sup> in 1863, demonstrated that the therapeutic efficacy of ipecac in amebiasis depended upon its alkaloid content which included principally emetine, cephalin, and psychotrine. Of these, the most powerful amebicide is emetine. The powerful amebicidal action of emetine was demonstrated, in 1912, by Vedder<sup>332, 334</sup> who found that amebae in vitro are killed readily by a solution of 1 to 100,000 dilution. Rogers<sup>321-324</sup> in the same year, reported the excellent results that may be obtained with this drug in the treatment of amebic hepatitis. Of historical interest in this connection is the fact that Maclean,<sup>326a</sup> as early as 1871, had directed attention to the value of ipecac in acute hepatitis and in preventing abscess formation. In 1913, James<sup>185</sup> demonstrated by careful experimental studies that emetine produces degenerative changes in the ameba and that the beneficial effect of the drug is due to its direct action upon the parasite. Subsequent investigators have corroborated these findings.<sup>102, 205, 336</sup> However, as shown by Craig,<sup>17, 85</sup> whereas the drug destroys the trophozoites even in great dilutions, it does not destroy the cysts except in quantities which cannot be administered safely. For this reason it is not the most effective drug in intestinal amebiasis. On the other hand, in amebic hepatitis and hepatic abscess incontrovertible evidence has demonstrated that it is the drug par excellence.

The demonstration by Rogers,<sup>326</sup> approximately three decades ago, that the mortality rate was decreased from 56.8 per cent to 14.4 per cent by the use of emetine and aspiration formed an important landmark in the therapeutic consideration of amebic hepatitis and hepatic abscess. Numerous observers subsequently confirmed his observations.<sup>124</sup> In 1917, Allen<sup>2</sup> reported that the admission rate for liver abscess fell from 2.4 to 1.4 per thousand troops, and the death rate from 1.3 to 0.48 per thousand within two years after adoption of ipecac by the British Army in India. Recently Spittel<sup>353</sup> reported a 73 per cent reduction in the incidence of liver abscess in the British Army and attributed this to the institution of early and adequate emetine therapy and to routine stool examinations. At present, it is the consensus of most authorities that emetine hydrochloride is the most valuable drug in amebic hepatic involvement and even large abscesses may completely disappear under emetine therapy alone.<sup>429</sup> As previously emphasized by us, every case of suspected amebic hepatitis or amebic abscess should be given the advantage of a course of emetine therapy before any other procedure is used unless rupture of the abscess appears imminent. In many cases, especially in those with early small abscesses, no other therapy will be required (Case 1). However, in the majority of cases it has been our experience that evacuation of the abscess contents will be necessary (Cases 2 and 3).

The significance of Rogers' contribution is better appreciated by a brief historical consideration of the treatment of hepatic abscess. In 1895, Matas<sup>40</sup> presented a succinct review of this subject and divided the history of treatment of liver abscess into three great periods: (1) "The purely medical period, during which the evacuation of the purulent collection was allowed to take place spontaneously." The mortality during this period, which embraced the history of medicine up to the sixth decade of the eighteenth century, was 80 per cent. (2) "The second epoch in the history of hepatic abscess may be said to be limited to the short period from 1860 to the early '70's, during which the early exploration with the aspirator gradually became the rule of practice, to be followed by repeated explorations and finally cautious opening with trocars or caustic pastes or by means of small incisions." (3) "The third period . . . begins with the '70's, when the Listerian discovery made the surgeons bolder in opening the peritoneal and pleural cavities in the effort to evacuate the abscess early." During this period the trocar "gradually yielded to the knife" and the "rule of surgical practice" consisted of "immediate evacuation by free incision regardless of situation or quantity of pus. . . ." That the mortality during this period was still very high is shown by Matas' report of 182 cases admitted to the Charity Hospital in New Orleans during the ten-year period, 1884 to 1894, with 87 (or 42.56 per cent) deaths. Thus, Rogers' epochal contribution may be considered as inaugurating the fourth and most important period in the treatment of amebic hepatitis and hepatic abscess.

The drug is preferably administered subcutaneously as emetine hydrochloride in daily doses of 0.065 Gm. (1 gr.) until 0.39 to 0.65 Gm. (6 to 10 gr.) have been given. Because of its toxicity in excessive dosages and its cumulative action the noxious effects of this drug should be realized and considerable care exercised in its use. Experimental investigations have shown that it is essentially a protoplasmic poison with an apparent selective action on muscle.<sup>37, 116, 405</sup> The danger of administering the drug in excessive dosage or over prolonged periods is indicated by the pronounced degenerative changes produced in cardiac musculature. Clinical manifestations of its toxicity consist of severe diarrhea, nausea and vomiting, profound prostration, cardiac arrhythmia and failure, muscular pains, and weakness especially in the extremities. According to Leake,<sup>207</sup> the maximum amount of emetine that should be given over any period of time should not exceed 10 mg. ( $\frac{1}{8}$  gr.) per kg. of body weight. Accordingly, for a patient weighing 150 pounds (about 68 kg.) this would be about 0.65 mg. (10 gr.). Other amebicides such as acetarsone, carbarsone, treparsol, chiniofon (anayodin and yatren), vioform, and diodoquin which are safer and more efficient in the treatment of intestinal amebiasis are not considered desirable in the treatment of amebic hepatitis and hepatic abscess because they are not as effective in these conditions as emetine and because, as

shown by Leake,<sup>208</sup> they are toxic to the liver. However, immediately following completion of therapy of the amebic hepatic condition the patient should be given a course of therapy for the intestinal amebiasis. Whereas frequently this cannot be demonstrated clinically, it should be assumed to exist once the diagnosis of amebic hepatitis and hepatic abscess has been established. Moreover, the therapy employed for the latter should not be considered adequate for the treatment of the intestinal infestation. For this reason a separate and different type of therapy should be employed for the intestinal amebiasis.

Aspiration is the procedure of choice in cases in which evacuation of the abscess becomes necessary. In these cases, however, it should be realized that the preliminary administration of emetine is important. In the Tulane Surgical Service, emetine hydrochloride is administered routinely in these cases in daily doses of 0.065 Gm. (1 gr.) for two or four days preceding the aspiration. Because the majority of amebic hepatic abscesses are sterile and because of the prognostic and therapeutic importance of this fact every attempt should be made to maintain this sterility. The evacuation of these abscesses by open drainage is invariably followed by secondary infection and the morbid consequences of this development have been previously emphasized. It is possible to evacuate the abscess and simultaneously maintain its sterility only by closed drainage. In the discussion under prognosis, the contrasting mortality obtained by the two methods convincingly demonstrates the obvious advantages of closed drainage. It will be recalled that in our series of cases open drainage was used in 80 with a mortality of 22.1 per cent and conservative therapy in 83 with only three deaths, a mortality incidence of only 3.6 per cent (Graph XIII). Of interest also is the fact that aspiration was performed without preliminary emetine in two of these three fatal cases and within a relatively short period of time following the procedure the patients developed manifestations of shock and died. The other patient was treated with emetine and anayodin on the medical service for almost three weeks and no attempt made to drain the hepatic abscess. At autopsy a huge hepatic abscess measuring approximately 20 cm. in diameter was found in addition to several smaller abscesses. We are firmly convinced that these three tragedies could have been averted, the first two by the preliminary administration of emetine and the third by aspiration of the abscess in addition to the use of emetine.

As previously emphasized, the procedure of aspiration should be performed in the operating room because the facility and reliability of strict asepsis are probably greater and because open drainage can be done immediately if the abscess is found to be secondarily infected. This may be determined readily by an immediate smear of the aspirated pus which in secondarily infected cases would reveal upon microscopic examination the presence of large numbers of bacteria and leucocytes. The technique of aspiration has been described above and the procedure

is performed in a similar manner for both diagnostic and therapeutic purposes (Figs. 22, 23, 24). The administration of emetine should be continued after closed drainage of the abscess until 0.39 to 0.65 Gm. (6 to 10 gr.) have been given. As previously stated by us, it is considered unnecessary as well as undesirable to introduce any substance into the abscess cavity as the use of irrigating solutions of amebicides has been found to be valueless.<sup>196-201, 203, 228, 262</sup>

Open drainage is usually necessary in secondarily infected cases as demonstrated by smear and culture. Of interest in this connection is the recent report of Alport and Ghaliougui<sup>1</sup> on the successful use of sulfonamides in a case of amebic hepatic abscess secondarily infected with *Bacillus pyocyaneus*. Accordingly even in the presence of secondary infection closed drainage was successfully employed. It is presumed that this was permitted by the use of sulfonamides. This is a promising development and if by this means it will be possible to employ closed drainage even in the secondarily infected cases the prognosis will be materially improved. Whereas this can be determined only by further experience, the sulfonamides should certainly be applied in all cases of secondarily infected amebic hepatic abscess. However, if open drainage becomes necessary it is imperative to institute that type of drainage which completely avoids the slightest possibility of contamination of the two virgin serous surfaces, i.e., the pleural and the peritoneal. In previous publications this phase of the subject was considered and the literature reviewed.<sup>244, 246</sup> In general the two types of drainage procedures which can be employed are transthoracic and transabdominal, either through a transserous or an extraserous approach. The transthoracic procedures were originally developed for the purpose of draining pyogenic abscesses of the liver or subphrenic spaces. In 1883, Trendelenburg<sup>277</sup> suggested this procedure and avoidance of contamination of the pleural cavity was attempted by suturing the costal and diaphragmatic layers of the pleura together. Several modifications<sup>226, 296</sup> of this procedure were subsequently advocated and of these probably the most popular is that of Beek<sup>15, 16</sup> who suggested, at the first stage operation, suturing the costophrenic pleural reflection and packing the wound for forty-eight hours with gauze impregnated with an irritative substance to produce adhesions, and at the second stage, incising through this area. Others<sup>109, 211, 245, 246, 296, 302</sup> have also attempted mobilization of the costophrenic angle upward, but as stated by Brown<sup>32</sup> this is frequently not satisfactory because of the firm adhesions resulting from the inflammatory reaction. As previously emphasized<sup>231</sup> such procedures are not only unnecessary, often unwarranted, frequently difficult, and deceptively dangerous, but in many instances definitely inadequate in protecting the virgin pleural cavity against invasion. The transperitoneal method of approach has similar disadvantages because it also permits contamination of uninvolved portions of the peritoneum. This is forcefully emphasized by graphic demonstrations of the contrasting

mortality statistics of the transserous and extraserous methods of drainage (Graph XV). Of 47 cases drained transpleurally, 7 had serious pleural involvement as determined by autopsy. Of the 7 deaths in the group in which patients were drained transperitoneally 6 developed generalized peritonitis and one died of spinal analgesia on the operating table. The one death in the group of patients drained extraserously has been described previously. This patient had multiple liver abscess with secondary infection and, following a second operation to drain other abscesses, developed pneumonia and died.

These facts demonstrate clearly the surgical rationale of the important principles, thoroughly appreciated over forty years ago,<sup>12,150, 256, 346, 367</sup> that drainage of such abscesses should be performed in such a manner that contamination of the pleural and peritoneal cavities is completely avoided. This may be accomplished best by an extraserous anterior or posterior approach, depending upon the location of the abscess. Accordingly, in those located anteriorly, the procedure described by Clairmont and Meyer<sup>62</sup> for drainage of subphrenic abscess should be employed. This consists briefly of making the skin incision just beneath and parallel to the costal margin, traversing the oblique muscles and transversalis fascia, and approaching the abscess extraperitoneally by carefully mobilizing the parietal peritoneum from the lower surface of the diaphragm.

In posteriorly located abscesses, on the other hand, the retroperitoneal approach previously described by us<sup>130</sup> is considered the most rational. This consists briefly in subperiosteally resecting the twelfth rib and entering the retroperitoneal space through a transverse incision made at the level of the spinous process of the first lumbar vertebra in the bed of the resected rib. The liver abscess is approached extraserously by carefully mobilizing the parietal peritoneum from the undersurface of the diaphragm. The comparatively low mortality of 6.6 per cent, i.e., only one death, in 15 cases of our series in which this procedure was employed convincingly demonstrated its value.

As previously stated in secondarily infected amebic hepatic abscess that is pointing, extraserous drainage may be done simply by incision over the point of greatest localization. Such a procedure in these cases becomes extraserous because the abscess has become walled off from the peritoneal cavity by involvement of the abdominal parietes. This method of drainage was possible in 19 of our cases, with two deaths, a mortality of only 10.5 per cent. The inadequate admission of emetine is believed to have been an important contributory factor in the death of these two patients. As previously emphasized, emetine therapy is just as important in cases requiring open drainage as in those in which closed drainage is used, and should be instituted in a similar manner.

It should be realized that following treatment of the amebic hepatic involvement it is essential to eliminate the intestinal infection. Failure to do this probably accounts for many recurrent abscesses. Since

emetine is not satisfactory for this purpose, other amebicides such as anayodin or diodoquin should be employed. The comparative value of these various amebicides is beyond the scope of this presentation and have been considered elsewhere.<sup>92, 237, 241, 266</sup>

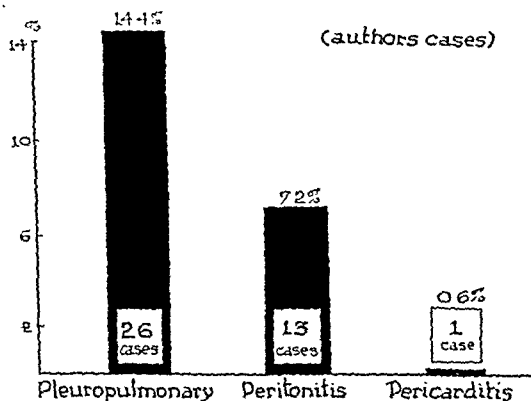
*Complications.*—The complications of amebic hepatic abscess consist essentially of secondary infection with pyogenic organisms, direct extension or rupture of the abscess into one of the adjacent viscera or serous cavities, and thrombosis and embolism. Their occurrence usually signifies negligence or procrastination on the part of the patient but occasionally reflects the physician's mismanagement. Thus, the development of peritonitis or empyema following that type of open drainage which does not completely avoid contamination of these virgin serous surfaces is obviously not due to the patient's disregard but is an example of the latter possibility. Moreover, lack of recognition of the condition sufficiently early undoubtedly accounts for the development of some of the complications. This is usually due to the absence of its consideration.

Pleuropulmonary involvement undoubtedly comprises the most frequent complication. In the majority of cases this is the result of either rupture or direct extension of the liver abscess through the diaphragm. Only a succinct discussion of the pertinent features of these complications will be given here as they have been extensively considered by us<sup>230</sup> in a previous publication. The incidence of pleuropulmonary involvement in amebic hepatic abscess varies considerably according to different observers. Thus, the low incidences of 3 and 3.1 per cent reported by Strong<sup>361</sup> and Harris,<sup>156</sup> respectively, are in direct contrast with the unusually high figures of 40.8 and 58.8 per cent recorded by Thompson<sup>370</sup> and Thierfelder,<sup>369</sup> respectively. In a collected series of 2,490 cases of amebic hepatic abscess pleural complications occurred in 198 (or 7.5 per cent) and pulmonary complications in 209 (or 8.3 per cent).<sup>230</sup> Thus, the combined incidence of pleuropulmonary complications was 15.8 per cent. In the previous series of 139 cases analyzed by us a similar incidence was obtained.<sup>237</sup> In the more recent series of 42 cases there were 5 cases with these complications.<sup>253</sup> Thus, in the total series of 181 cases, pleural complications occurred in 9 (or 5 per cent) and pulmonary in 17 (or 9.4 per cent) giving a total incidence of 14.4 per cent (Graph XVI). Of the 26 cases with pleuropulmonary involvement 8 (or 30.7 per cent) developed bronchohepatic fistula, 9 (or 34.6 per cent) empyema, and 9 (or 34.6 per cent) pulmonary abscess.

Pleuropulmonary amebiasis is occasionally due to systemic invasion but most commonly results from direct extension of an amebic hepatic abscess. Whereas it is doubtful whether primary infection of the lung without an antecedent infection of the bowel ever occurs, pulmonary metastatic lesions resulting from invasion of the systemic circulation apparently do occur rarely. Examples of the former possibility include cases of primary amebic bronchitis and pneumonitis reported by several



observers.<sup>111</sup> The occurrence of pleuropulmonary amebiasis resulting from systemic invasion by the ameba is convincingly demonstrated by the recent report of Girgis<sup>120</sup> who described two fatal cases of multiple amebic abscesses of the lung associated with multiple liver abscesses and active amebic dysentery in which the "whole series of events, . . . , including both the gross and histologic findings, may be taken as strong evidence for blood-borne amebic infections of the lungs from the liver through the right side of the heart to the lungs where we have actually found entamoebae in the emboli contained in the pulmonary arterial branches as well as in the abscess cavities." Cantlie,<sup>102</sup> in 1904, had directed attention to the possible embolic origin of some amebic lung abscesses. It is the consensus of most authorities, however, that pleuropulmonary amebiasis is most commonly the result of direct extension from an amebic hepatic abscess and follows usually perforation through the diaphragm but rarely transphrenic immigration via the lymphatics.<sup>213</sup> The location and virulence of the amebic hepatic infection probably explain the frequency of pleural and pulmonary complications.



Graph XVI.—Relative incidences of various complications in authors' cases of amebic hepatic abscess.

The majority of amebic hepatic abscesses develop near the convex surface and in the posterior portion of the right lobe. As the abscess enlarges the adjacent diaphragm becomes incorporated in the wall of the abscess facilitating its extension into the thoracic cavity. Involvement of the pleural cavity or lung parenchyma is probably influenced by the acuteness or chronicity of the hepatic process. Accordingly, an abscess which develops slowly is likely to produce an accompanying pleurisy with adhesions which would tend to obliterate the pleural cavity and thus permit rupture into the base of the right lung (Case 4). On the other hand, if the abscess progresses rapidly the preceding pleural reaction may not be sufficiently extensive to produce obliterating adhesions and the abscess ruptures into the pleural cavity (Case 5). Not infrequently rupture into the lung parenchyma produces a bronchial fistula and the abscess contents are evacuated by coughing (Case 4).

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grams with its base toward the liver and its apex extending toward the hilum of the lung (Figs. 11 to 15). There is also an increased density in the lower lung field. In cases in which the hepatic abscess ruptures into the pleural cavity the roentgenographic picture is that of pleural effusion (Figs. 18 to 20). By the use of such contrast substances as iodized oil introduced into the trachea a bronchohepatic fistula may be readily visualized in the roentgenogram (Fig. 16).<sup>59</sup>

The diagnosis of these complications is usually not difficult if the condition is considered. In addition to the characteristic pulmonary manifestations, evidence of hepatic involvement is usually present. Because of the frequent chronicity and the presence of bloody sputum the condition is likely to be confused with tuberculosis. It should be realized, however, that whereas a tuberculous lesion most commonly occurs in the apex, in amebic involvement the lesion is generally at the base and associated with hepatic involvement. Moreover, sputum examination should exclude tuberculosis and the demonstration of amebae should establish the diagnosis. The diagnosis may be suspected further by the characteristic roentgenographic findings (Figs. 11 to 15, and 18 to 20). The expectoration of characteristic chocolate-sauce pus is pathognomonic (Case 4). In the cases with pleural involvement aspiration of the pleural cavity usually reveals the pus (Case 5).

The prognosis in these complications is influenced by several factors including the type of involvement and therapy employed. The prognosis is worse in those cases in which the hepatic abscess ruptures into the pleural cavity and is best in those in which a bronchohepatic fistula develops with minimal pulmonary reaction. Moreover, in the latter cases the prognosis is not as good in those in which a small communication with the bronchus and a great lung reaction exist as in those with a large communication which permits rapid evacuation.<sup>252</sup> In the former, type of incomplete evacuation and the presence of secondary infection increase the gravity of the condition. The prognostic influence of the type of involvement is clearly demonstrated by respective mortality rates. Thus, in the collected cases the mortality was 77.7 per cent in the liver abscess with empyema and 43.2 per cent in liver abscess with extension into the lung, whereas it was only 10 per cent in liver abscess with bronchohepatic fistula. This contrast is even more pronounced in our series of 26 cases. Whereas of 8 cases with bronchohepatic fistula none died, of 9 cases with empyema 6 (or 66.6 per cent) died and of 9 cases with lung extension 2 (or 22.2 per cent) died (Graph XVII). The total mortality in our series was 30.8 per cent which is somewhat similar to that (28.5 per cent) reported by Huard and Meyer-May<sup>174</sup> in their series of 21 cases. The prognostic significance of the type of therapy is demonstrated by the fact that in the collected series the mortality was 56.1 per cent in those not receiving emetine and 9.1 per cent in those treated with emetine. These respective figures in our series were 60 per cent and 0. The treatment of these pleuropulmonary com-

In a previous publication we<sup>280</sup> presented a review of the literature and an analysis of 153 collected and 15 personal cases of pleuropulmonary amebiasis. Based upon this study pleuropulmonary amebic infections were classified into five types depending upon their gross pathologic characteristics: (1) hematogenous pulmonary abscess without liver involvement (14.3 per cent of the collected cases and none of the authors were of this type); (2) hematogenous pulmonary abscess and independent liver abscess (10.4 per cent of the collected cases and none of the authors' were of this type); (3) pulmonary abscess extending from liver abscess (these comprised 37.2 per cent of the collected and 34.6 per cent of our cases); (4) bronchohepatic fistula with little pulmonary involvement (this occurred in 19.6 per cent of the collected cases and 30.7 per cent of ours); and (5) empyema extending from a liver abscess (these formed 17.6 per cent of the collected and 34.6 per cent of our cases). It may be observed, therefore, that almost four-fifths of the cases result from direct extension of a hepatic process.

The clinical manifestations of pleuropulmonary amebiasis vary with the extent and mode of infection. The most common complaint is pain in the lower portion of the right chest with frequent radiation to the shoulder.<sup>12, 370</sup> This may be explained on the basis of involvement of the diaphragmatic pleura. This is especially pronounced by extension of the amebic hepatic abscess upward. The pain is sometimes described as sharp, stabbing, or shooting in character and occasionally is violent and aggravated by coughing or deep inspiration.<sup>309</sup> Another prominent symptom is an annoying unproductive cough which occurs particularly in the beginning. Dyspnea may be present especially when a large abscess produces considerable encroachment upon the lung field. Not infrequently the symptoms become suddenly more pronounced and the patient begins to cough up large quantities of purulent material and particularly chocolate-sauce pus which is pathognomonic of a hepatobronchial fistula. A carefully performed sputum examination will frequently reveal the ameba and establish the diagnosis. Other common manifestations are fever usually more pronounced than in uncomplicated amebic hepatic abscess, anorexia, malaise, weakness, and loss of weight. The chest findings may vary but usually are characteristic of consolidation and cavitation especially at the base of the right lung. In those cases which rupture into the pleural cavity there are characteristically present manifestations of pleural effusion. The pleurisy and pleural effusion which precede the rupture represent a contiguous inflammatory reaction.<sup>4</sup> There is usually a moderate leucocytosis which is more pronounced in those cases which rupture into the pleural cavity and less in the hepatobronchial fistula cases.

Roentgenographic examination is of particular diagnostic significance in these complications. Aside from the fluoroscopic demonstration of elevation and immobilization of the diaphragm there is characteristically a triangular shadow in both the anteroposterior and lateral roentgeno-

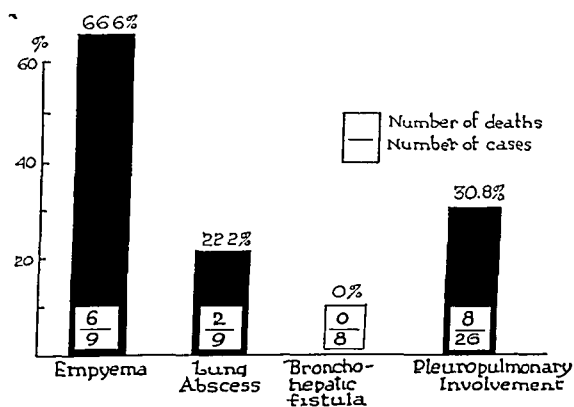
cesses (Graph XVI). It is interesting to observe that whereas in the previous series of 139 cases the incidence of this complication was 7.9 per cent, in the more recent series of 42 cases the incidence dropped to 4.7 per cent.

Depending upon the type of development, amebic hepatic abscesses that rupture into the peritoneal cavity produce localized or generalized peritonitis. Most of these develop by gradual extension of the abscess to the periphery of the inferior surface of the liver stimulating a peritoneal reaction and permitting the formation of peritoneal adhesions and consequent localization. On the other hand, if the abscess extends and enlarges more rapidly, especially if secondary infection develops, and particularly if there is a precipitating factor such as trauma or exertion, perforation and rupture of the abscess may occur into a virgin peritoneal cavity producing a generalized peritonitis. Accordingly, the clinical manifestations will vary. Whereas in the former type in which a previous peritoneal reaction has permitted walling off of the abscess resulting in relatively mild manifestations, in the latter in which rupture occurs into a virgin peritoneal cavity with good absorbability, severe clinical manifestations are produced by the rapid absorption of the toxic material. The danger of sudden rupture of an abscess into a virgin peritoneal cavity has been emphasized previously.<sup>276</sup> Because of this rapid absorption of the toxic material, the clinical manifestations in these cases are characteristically those of shock. Following the experience of sudden intense abdominal pain the patient appears anxious, the face flushed, the pulse rapid and feeble, the blood pressure drops, the temperature begins to rise precipitously, generalized abdominal tenderness and rigidity become manifest, and there is all the evidence of an acute abdominal catastrophe. Whereas the manifestations may not be as severe as in primary pyogenic infections, nevertheless the prognosis is relatively bad. Thus, in a collected series of 46 cases there were 28 (or 60.8 per cent) deaths.<sup>1</sup> Loubet<sup>217</sup> reported 11 cases with 3 (or 27.3 per cent) deaths. In our series of 13 cases there were 10 (or 77 per cent) deaths. In the case with localized peritonitis the prognosis is better.

The presence of a localized or generalized peritonitis also influences the therapy, although emetine should be administered in all cases. In the former aspiration should be done first and if secondary infection is demonstrated, immediate open drainage should be instituted. This is necessary in the majority of cases and was done in the three cases of our series. In the remaining cases the patients died soon after the onset of generalized peritonitis. Biggam and Rajol<sup>23</sup> advocate conservative therapy consisting of aspiration of the peritoneal fluid and the administration of emetine. On the other hand, Loubet<sup>215</sup> prefers drainage by operation.

Occasionally an amebic hepatic abscess may rupture into the pericardial cavity. This unusual complication occurs in less than 2 per cent

plications is governed by the type of involvement. Emetine should be administered in all cases just as described above in the treatment of uncomplicated hepatic lesions and its inestimable value has been emphasized previously.<sup>233, 280</sup> Conservative therapy consisting of emetine administration and postural drainage is usually sufficient in the bronchohepatic fistula type in which the communication is sufficient to permit rapid evacuation (Case 4). In some cases bronchoscopic drainage as suggested by Pellé<sup>303</sup> may be of value. The superiority of conservative therapy is shown by the fact that all of the cases in our series treated in this manner recovered, whereas only about a third of those operated upon recovered. More recently the value of conservative therapy has been emphasized by several observers.<sup>7, 100, 147, 195, 344</sup> However, operation may be necessary in certain cases. Thus, in those associated with an empyema aspiration should be done first and if secondary infection is demonstrated open drainage should be instituted.<sup>40b, 40c, 40d, 203, 280</sup> However, if secondary infection is not demonstrable, conservative therapy should be maintained (Case 5).



Graph XVII.—Relative mortality incidences in authors' cases of pleuropulmonary involvement according to type of lesion.

Extension into the peritoneal cavity is the next most frequent complication of an amebic hepatic abscess. The incidence varies according to different authors. Thus, Cyr<sup>100</sup> reported this eventuality in 6.9 per cent of 563 cases, Ludlow<sup>218</sup> in 5 per cent of 100 cases, Huard and Meyer-May<sup>174</sup> in 3.3 per cent of 150 cases, Jayasuriya<sup>188</sup> in 2.7 per cent of 73 cases, and Peiris<sup>302</sup> in 7.1 per cent of 28 cases. In a collected series of 1,095 cases, including ours, the hepatic abscess ruptured into the peritoneal cavity in 66 (or 6 per cent).<sup>90, 174, 195, 218, 302</sup> Vergoz and Hermanjat-Gerin<sup>384</sup> found that of 80 cases of ruptured amebic abscess, 39 (or 48.7 per cent) were into the peritoneal cavity. Of 46 cases analyzed by Acebal<sup>1</sup> there were 24 with generalized peritonitis and 22 with localized peritonitis. In our series of 181 cases of amebic hepatic abscess there were 13 (or 7.2 per cent) that ruptured into the peritoneal cavity and this comprised one-third of the total number of ruptured hepatic ab-

the rational conception and specific therapy of amebiasis these complications should seldom if ever occur.

### ILLUSTRATIVE CASE REPORTS

The following case is a characteristic example of an amebic hepatitis with satisfactory response to conservative therapy. This is considered to be in the "presuppurative" stage and by the use of emetine progression to abscess formation is prevented. Upon admission the diagnosis was not clear and certain features indicated the possibility of bronchopneumonia and pleurisy. For this reason he was placed on sulfapyridine therapy. It soon became apparent that this diagnosis was incorrect and the presence of amebae in the stool suggested the correct diagnosis which was confirmed by the dramatic response to emetine therapy.

**CASE 1.**—R. J., a colored male, 33 years of age, was admitted to Charity Hospital on Feb. 3, 1940, and discharged on Feb. 23, 1940.

**Chief Complaint**—Sharp pain in right lower chest and upper abdomen

**Present Illness**—The patient stated that his illness began on Jan. 30, 1940, at which time he had a pain high in the epigastrium. This was a drawing type of pain associated with a fullness in the abdomen. The pain developed gradually and was soon accompanied by slight nausea. The patient had to gag himself with his fingers to vomit, but the nausea was not relieved by vomiting. The pain in the epigastrium and the nausea persisted for several days and then he developed chills and fever. The next day the patient went to work as usual in a lumber yard, but felt very tired and his back ached severely. He claims that his joints ached so much that he could not bend his knees. The following night a severe, sharp pain struck him in the right hypochondriac region. The pain was so severe that it caused him to double up. Deep breathing aggravated the pain which sometimes radiated to the right shoulder. He remained in bed until he came to the hospital. After admittance he had a bad cold and a running nose for about a week. He coughed occasionally. The cough was slightly productive of white watery sputum. His appetite has been good until the writing of this report. He had a history of chronic constipation but no diarrhea except occasionally a loose stool.

**Physical Examination**—Pulse, 100, respiration, 24; blood pressure, 140/80; temperature, 102° F. The patient was apparently not acutely ill, he lay quietly in bed on a back rest, but with a tired, worried facies. Examination of the chest revealed no significant findings except a slight rig in the right lower portion, and extreme tenderness in this area as well as decreased resonance, decreased breath sounds, and occasional dry rales. The abdomen appeared flat, muscular, and somewhat rigid. Extreme tenderness was elicited just below the costal margin on the right side and over the liver which was palpable two fingerbreadths below the right costal margin.

**Laboratory Findings**—On Feb. 3, 1940, hemoglobin was 75 per cent, red blood cells, 4,100,000, white blood cells, 24,000, polymorphonuclears, 84 per cent, lymphocytes, 14 per cent. On April 7, 1940, red blood cells were 3,333,000, white blood cells, 17,400, polymorphonuclears, 84 per cent, lymphocytes, 10 per cent, monocytes, 5 per cent, urinalysis, no abnormal findings. Blood chemistry was normal, and on Feb. 8, 1940, sulfapyridine level, 12, blood Wassermann, negative; sputum, negative for all types of pneumococci and for acid fast organisms. Stool examination on Feb. 15, 1940, showed cysts of *L. histolytica* and blood culture, negative. Roentgenographic studies of the chest on Feb. 7, 1940, showed slight thickening of the pleura in the right costophrenic angle and of the right intralobar pleura but no evidence of pneumonia or encapsulated fluid. The impression was thickened pleura.

of the cases. In Huard and Meyer-May's<sup>174</sup> series of 150 cases it was present in 3 (or 2 per cent) and in our series of 181 cases it occurred in only 1 (or 0.6 per cent) (Graph XVI). Of 80 ruptured amebic hepatic abscesses reported by Vergoz and Hermenjat-Gerin,<sup>384</sup> 13 (or 16.2 per cent) perforated into the pericardium. They are more likely to follow abscesses of the left lobe of the liver, which are more difficult to recognize. Clinically this complication is characterized by sudden manifestations of pyopericardium with a rapidly fatal termination. All of Vergoz and Hermenjat-Gerin's<sup>384</sup> cases were fatal as were ours. However, a few recoveries have been reported. Huard and Meyer-May<sup>173</sup> recorded a patient who recovered following open drainage and more recently Purcell<sup>310</sup> reported a case in which conservative therapy consisting of emetine and aspiration was apparently successful.

There are still other rarer complications of amebic hepatic abscess, most of which consist of perforation. Accordingly, cases have been reported in which the abscess ruptured into the gastrointestinal tract,<sup>51, 66, 188, 223, 261</sup> into the suspensory ligament,<sup>307</sup> through the abdominal wall,<sup>59, 174, 218, 302</sup> into the biliary tract,<sup>29, 69, 96</sup> and into the portal vein and inferior vena cava.<sup>26, 56, 64, 120, 132, 224</sup> Perforation or drainage of an amebic hepatic abscess through the abdominal wall is one of the most frequent causes of cutaneous amebiasis and comprises from one-third to one-half of the cases of this type of amebiasis.<sup>111, 179, 236, 267, 376, 400</sup> We have previously reviewed this subject.<sup>282-284</sup> The condition is characterized by progressive necrosis and ulceration of the skin. The treatment consists essentially of radical excision and administration of emetine.

Other even rarer complications are cerebral abscess and extension of an amebic hepatic abscess into the spleen and the kidneys. Kartulis<sup>192</sup> found brain abscesses in 3 per cent of the cases of amebic dysentery in Egypt, and Izar<sup>184</sup> collected 56 cases of amebic abscesses of the brain, 29 of which occurred in Egyptians. Cerebral abscess is considered the result of blood-borne infection and hepatic and pleuropulmonary involvement are frequent antecedent lesions.<sup>311</sup> Runyan and Herrick<sup>335</sup> reported a case of amebic cerebral abscess which occurred shortly after drainage of a liver abscess and sponging of the cavity with gauze. The condition is almost invariably fatal. Of the 59 cases collected by Huard<sup>170</sup> all terminated fatally. The rarity of splenic involvement is shown by the fact that Huard<sup>170</sup> was able to collect only 6 cases from the literature. It may be due to metastasis from the intestine or to direct extension of an amebic abscess of the left lobe of the liver. Kidney lesions are also extremely rare. These complications are usually determined at autopsy and are associated with the more severe extensive and neglected cases of amebiasis.

As previously stated, it is significant that most of these complications occurred in the earlier reported cases. At the present time because of



The following case is a characteristic example of an amebic hepatic abscess that responded satisfactorily to conservative therapy consisting of emetine and aspiration of the abscess. In this case the clinical manifestations were quite characteristic, including the history of an antecedent diarrhea although stool examinations were negative. The clinical diagnosis of amebic hepatic abscess was fairly evident and supported by the characteristic roentgenographic findings. The diagnosis was definitely established by the aspiration of typical chocolate-sauce pus as well as the patient's dramatic response to this conservative therapy.

CASE 2.—C. L., a white male, 56 years of age, was admitted to Charity Hospital on Jan. 2, 1941, and discharged on Jan. 28, 1941.

*Chief Complaint.*—Pain in the upper right abdomen for one and one-half months.

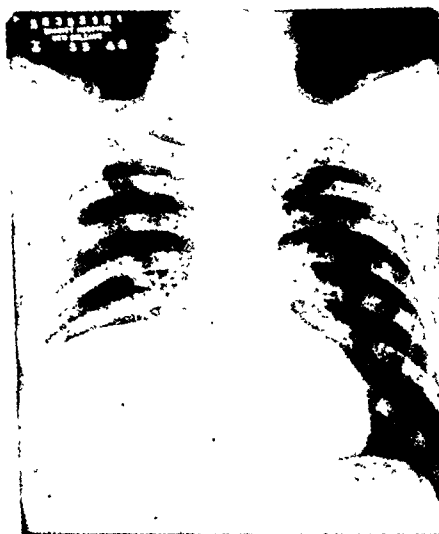


Fig. 5.

Fig. 5.—Anteroposterior roentgenogram of chest with amebic hepatic abscess showing elevation and bulging of right leaf of diaphragm and obliteration of cardiophrenic angle.



Fig. 6.

Fig. 6.—Lateral roentgenogram of chest of patient referred to in Fig. 5 showing pronounced elevation and bulging upward of right leaf of diaphragm and obliteration of anterior costophrenic angle.

*Present Illness.*—Patient states that about three months previously he had an attack of diarrhea with twenty to thirty bowel movements daily, associated with tenesmus and mucus in the stools. Upon seeing his physician he was told to change his diet and was given medicine to relieve the diarrhea. This lasted for approximately two months and during the past month he has had fever, and pain and tenderness in the right upper abdominal quadrant. He also complains of anorexia, loss in strength, and considerable loss in weight.

*Physical Examination.*—Blood pressure, 120/75; temperature, 101° F.; pulse, 130; and respiration, 28. The general appearance was that of a poorly nourished man, resting quietly in bed, and not apparently acutely ill. Significant findings were limited to the lower right chest and abdomen. There seemed to be a slight

On Feb. 16, 1940, views of the chest show clear lung fields, but there is elevation of the right leaf of the diaphragm and apparent thickening of the pleura in the right axillary region with slight obliteration of the cardiophrenic angle in the posteroanterior view (Fig. 2), and a distinct bulging of the diaphragm and obliteration of the anterior costophrenic angle in the lateral view (Fig. 3).

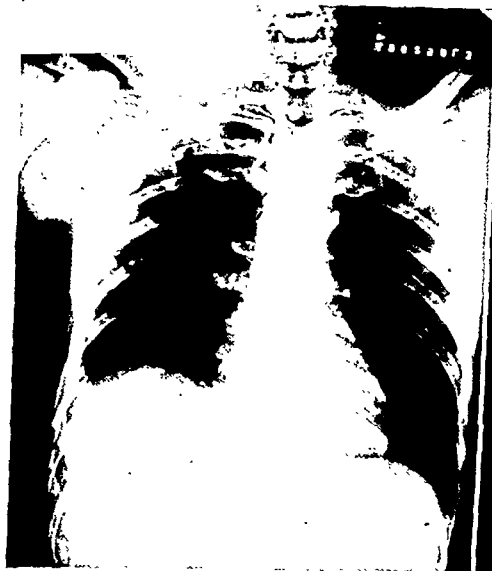


Fig. 2.



Fig. 3.

Fig. 2.—Anteroposterior roentgenogram of chest of patient reported in Case 1 with amebic hepatitis showing characteristic elevation of right leaf of diaphragm with obliteration of cardiophrenic angle.

Fig. 3.—Lateral roentgenogram of chest of patient referred to in Fig. 2 showing characteristic elevation and slight bulging of right leaf of diaphragm with obliteration of anterior costophrenic angle.

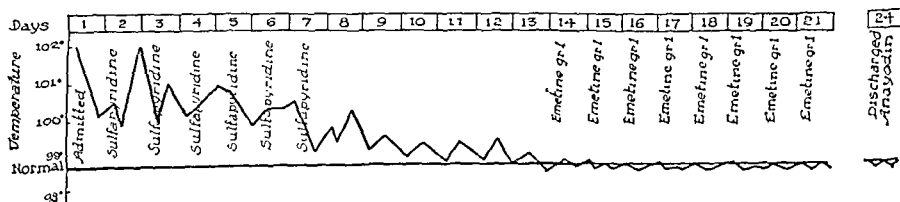


Fig. 4.—Temperature chart of patient in Case 1 showing little response to sulfapyridine but dramatic response to emetine.

**Clinical Course.**—The patient was admitted to the ward with the diagnosis of pleurisy with effusion and pneumonitis. He was given sulfapyridine for approximately one week but the clinical manifestations were not remarkably relieved although the temperature curve showed a slight decrease (Fig. 4). Following the demonstration of *E. histolytica* cysts in the stools and characteristic roentgenographic findings on Feb. 16, 1940, a tentative diagnosis of amebic hepatitis was made and the patient was given emetine hydrochloride, gr. 1, daily for one week. Immediately after instituting this therapy the temperature dropped to normal and remained there until his discharge (Fig. 4). The clinical manifestations were completely relieved and upon his discharge he was placed on anayodin therapy for intestinal amebiasis.

CASE 3.—M. J., a colored female, 34 years of age, was admitted to Charity Hospital on May 2, 1942, and discharged on June 14, 1942.

*Chief Complaint.*—The chief complaint of the patient was pain in the right upper abdomen.

*Present Illness.*—About two weeks prior to admission the patient began having pain in the right upper abdomen. It was dull aching in character, gradually becoming worse, and particularly aggravated by deep breathing. One week later she began having nausea and vomiting and some fever. During the six weeks prior to admission she had lost about eighteen pounds in weight. Her appetite had steadily diminished and she had lost strength. About a year ago she had "loose bowels" and passed blood in her stools. This attack lasted about a week and since then she has had no bowel disturbances.

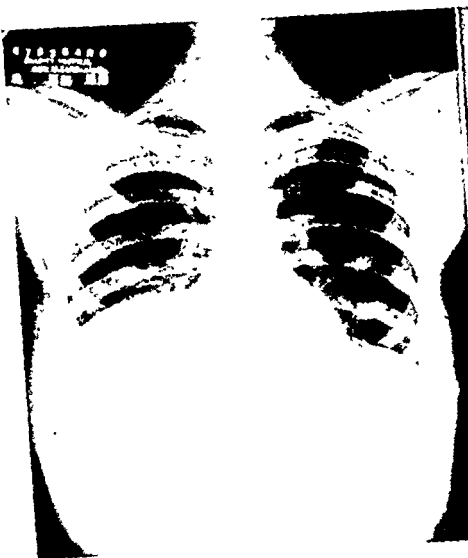


Fig. 8.



Fig. 9.

Fig. 8.—Anteroposterior roentgenogram of chest of patient reported in Case 3, showing pronounced elevation of right leaf of diaphragm and obliteration of cardiophrenic angle.

Fig. 9.—Lateral roentgenogram of chest of patient referred to in Fig. 8, showing elevation of right leaf of diaphragm and obliteration of anterior costophrenic angle.

*Physical Examination.*—Temperature was 100.6° F.; pulse, 100; respiration, 24; blood pressure, 110/76. General observations: the patient was slightly undernourished, ambulatory, and not acutely ill. The significant findings were limited to the lower right chest and abdomen. There was some lag of the right chest and the liver dullness extended up to the fourth interspace. There was distinct muscular rigidity in the right upper abdominal quadrant and acute tenderness over this area, especially along the right anterior costal margin. The liver was palpable about three fingerbreadths below the right anterior costal margin.

*Laboratory Findings.*—On May 5, 1942, hemoglobin was 70 per cent; red blood cells, 3,400,000; white blood cells, 14,760; polymorphonuclears, 76 per cent; lymphocytes, 15 per cent; monocytes, 7 per cent; eosinophiles, 2 per cent; and urinalysis showed a slight trace of albumin. The blood chemistry was normal, Wassermann, negative, and stool examination revealed cysts of *E. histolytica*. Roentgenographic studies showed distinct immobilization and elevation of the right leaf of the diaphragm with obliteration of the cardiophrenic angle in the posteroanterior view (Fig. 8) and the anterior costophrenic angle in the lateral view (Fig. 9).

lagging of the right chest and liver dullness extending higher than normal. There was marked tenderness along the right costal margin, and some rigidity over the hepatic area. The liver was enlarged two fingerbreadths below the right costal margin.

**Laboratory Findings.**—On Jan. 5, 1941, hemoglobin was 65 per cent; red blood cells, 3,550,000; white blood cells, 22,300; polymorphonuclears, 90 per cent; lymphocytes, 8 per cent; monocytes, 2 per cent. On Jan. 7, 1941, white blood cells were 16,500; polymorphonuclears, 85 per cent; lymphocytes, 14 per cent; monocytes, 15 per cent; and urinalysis, negative. Blood chemistry was normal and blood Wassermann negative. On Jan. 31, 1941, pus from liver abscess showed no parasites and no bacterial organisms. Stool examinations on three occasions, January 4, 6, and 13, showed no ova or parasites. Roentgenographic examination of the chest, Jan. 2, 1941, showed elevation of the right leaf of the diaphragm and atelectasis at the right base. Subsequent views of the chest showed immobilization, elevation, and localized bulging of the right leaf of the diaphragm with obliteration of the cardiophrenic angle in the posteroanterior view (Fig. 5), and obliteration of the anterior costophrenic angle in the lateral view (Fig. 6).

**Clinical Course.**—Following the characteristic roentgenographic findings a tentative diagnosis of amebic hepatic abscess was made and the patient started on emetine therapy. Two days later, under local analgesia, aspiration of the liver was performed and 700 c.c. of chocolate-sauce pus were removed from the liver abscess. The day after the aspiration the patient's temperature which had been ranging between 99° and 101° F. dropped to normal and remained there (Fig. 7) until his discharge from the hospital and he was completely relieved of all previous manifestations. Upon his discharge he was placed on diodoquin therapy for intestinal amebiasis.

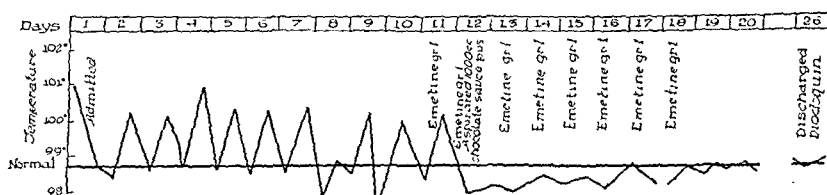


Fig. 7.—Temperature chart of patient in Case 2 showing moderate irregular pyrexia and dramatic response to emetine and aspiration therapy.

The following case is an example of amebic hepatic abscess which was at first believed to be an amebic hepatitis. The clinical manifestations of an amebic hepatitis were quite characteristic, including an antecedent dysentery and the presence of ameba in the stools. The roentgenographic findings were also characteristic. Accordingly a diagnosis of amebic hepatitis was made and the patient placed on emetine therapy. Her immediate response was dramatic; the temperature dropped to normal and she was remarkably improved. However, within about one week after beginning this therapy there was a slight recurrence of fever which was increasing and the hepatic tenderness although diminished was still present. It was soon evident that the pathologic process had progressed beyond a simple hepatitis to true abscess formation. This was definitely established by the aspiration of typical chocolate-sauce pus and the subsequent complete relief of all manifestations.

mitted to the hospital on several occasions and the diagnosis was not suspected until after he began coughing up characteristic chocolate-sauce pus. The diagnosis of bronchohepatic fistula was definitely established by roentgenograms taken after intratracheal instillation of lipiodol. The satisfactory response to conservative therapy and postural drainage is clearly demonstrated.

CASE 4.—L. A., a colored male, 45 years of age, was admitted to the hospital on April 11, 1941.

*Chief Complaint.*—There was pain in the right chest, cough and expectoration of bloody mucus.



Fig. 13.

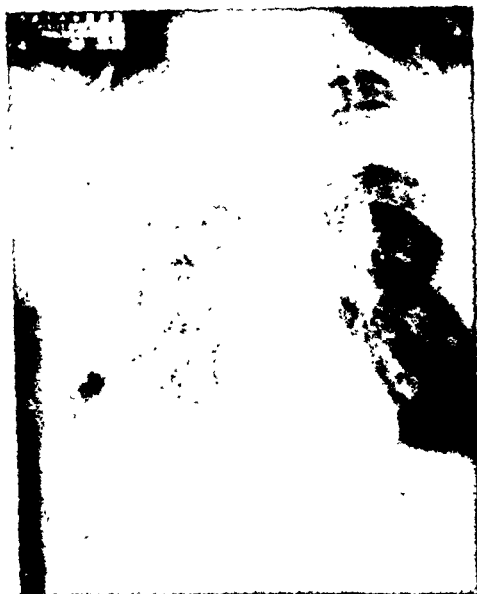


Fig. 14.

Fig. 13.—Lateral roentgenogram of chest of patient referred to in Fig. 12 and taken at same time, i.e., several days after amebic hepatic abscess had ruptured into lung. In contrast with that taken before rupture as shown in Fig. 11, it will be observed that the apex of the localized bulging is now less distinct and extends up to the hilum of the lung.

Fig. 14.—Anteroposterior roentgenogram of chest of patient reported in Case 1 with amebic hepatic abscess and bronchohepatic fistula. There is definite elevation of the right leaf of the diaphragm, obliteration of the cardiophrenic angle, characteristic triangular shadow with the apex pointing into the lower lung field, and evidence of right pneumonitis.

*Present Illness.*—The patient stated that he first became ill in July, 1939, with malaise, night sweats, weakness, and expectoration of blood-stained mucus. He also had pain in the right chest. He came to Charity Hospital in August, 1939, and remained there for about one month. He left the hospital feeling much better but was readmitted on several occasions since then with the same complaints. He has continued to cough and expectorate a dark reddish mucopurulent material which is sometimes tinged with bright blood. He lost about thirty-five pounds in weight since the onset of his illness. At the time of the writing of this communication, his appetite was good and he had no digestive disturbances.

*Physical Examination.*—Temperature was 102° F.; pulse, 90; respiration, 22, and blood pressure, 105/60. General observation revealed a somewhat undernourished

**Clinical Course.**—A diagnosis of amebic hepatitis was made and the patient placed on emetine therapy, 1 gr. daily for 10 days. Within four days the temperature dropped to normal and remained there for about one week and then there was slight recurrence of fever (Fig. 10). Although there was considerable improvement clinically the patient still complained of some pain and tenderness over

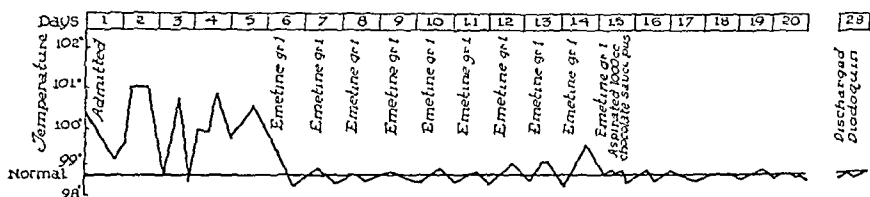


Fig. 10.—Temperature chart of patient in Case 3 showing definite response to emetine therapy with slight recurrence of fever which completely disappeared following aspiration of 1,000 c.c. of chocolate-sauce pus.



Fig. 11.

Fig. 11.—Lateral roentgenogram of chest of patient with amebic hepatic abscess made several days before rupture into lung. The obliteration of the anterior costophrenic angle and the localized upward bulging of the diaphragm are characteristic features.

Fig. 12.—Anteroposterior roentgenogram of chest of patient referred to in Fig. 11 taken several days after amebic hepatic abscess had ruptured into lung and patient began coughing up chocolate-sauce pus. There is a pronounced elevation of the right leaf of the diaphragm and obliteration of the cardiophrenic angle with the apex of a triangular shadow extending toward the hilum of the lung. The edges of the shadow are less sharply defined than in that taken before rupture, probably due to the associated pneumonitis.

the hepatic area. It was decided that the patient had a true abscess and this was subsequently verified by the aspiration of 1000 c.c. of chocolate-sauce pus. Immediately following this procedure the temperature dropped to normal and remained there until the patient was discharged when she was placed on diodoquin therapy (Fig. 10). All previous manifestations were completely relieved.

The following case is a characteristic example of an amebic hepatic abscess which ruptured into the bronchus. This patient had been ad-

*Clinical Course.*—On the basis of the characteristic clinical manifestations and the roentgenographic findings a diagnosis was made of amebic abscess of the liver with rupture into the lung and development of hepatobronchial fistula. The patient coughed up characteristic chocolate-sauce material. Therapy consisted of postural drainage and the administration of emetine hydrochloride, gr. 1, daily for nine days. He responded satisfactorily with the temperature (Fig. 17) dropping to normal and remaining there until his discharge and complete relief of manifestations.

The following case is an example of an amebic hepatic abscess that ruptured into the right pleural cavity. The clinical manifestations and the roentgenographic findings at first suggested the diagnosis of bronchopneumonia with pleural effusion and the patient was treated with sulfathiazole. His response was not satisfactory and the correct diagnosis



Fig. 18.



Fig. 19.

Fig. 18.—Anteroposterior roentgenogram of the chest of the patient reported in Case 5 showing opacity of right hemithorax in the lower two-thirds due to rupture of amebic hepatic abscess into pleural cavity.

Fig. 19.—Lateral roentgenogram of the chest of the patient referred to in Fig. 18 and taken at the same time. The right leaf of the diaphragm cannot be delineated.

was suggested by the finding of ameba in the stools and the demonstration by thoracentesis of chocolate-sauce pus in the right pleural cavity. Since smear and culture studies revealed the pus, sterile conservative therapy consisting of emetine and aspiration evacuation was instituted. The satisfactory response to this therapy is clearly demonstrated.

CASE 5.—P. L., a colored male, 30 years of age, was admitted to Charity Hospital on Aug. 25, 1941.

*Chief Complaint.*—Pain in the right chest was the chief complaint of the patient.

*Present Illness.*—The patient stated that about two weeks prior to admission he experienced a sudden sharp pain in the right upper abdomen and lower chest while

negro male apparently chronically ill. Significant findings were limited to the chest and abdomen. There was slight lagging of the right chest. The breath sounds on the right side were diminished in the lower part with dullness and moist râles in this area. Examination of the abdomen revealed tenderness immediately below the right costal margin. The liver was not palpable.



Fig. 15.



Fig. 16.

Fig. 15.—Lateral roentgenogram of chest of patient referred to in Fig. 11 showing definite elevation of right leaf of diaphragm, obliteration of anterior costophrenic angle, and a characteristic triangular shadow with its apex projecting toward the hilum of the lung.

Fig. 16.—Lateral roentgenogram of intratracheal lipiodol instillation of chest of patient referred to in Figs. 11 and 12 showing bronchohepatic fistula. The lipiodol can be traced through the apex of a triangular shadow and beneath the diaphragm into the liver abscess.

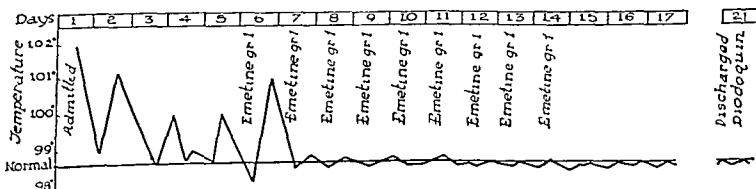


Fig. 17.—Temperature chart of patient in Case 4 showing definitive response to postural drainage and emetine therapy.

**Laboratory Findings.**—Urinalysis was negative, Wassermann, negative and blood culture, negative. Sputum showed no parasites and no acid-fast organisms. Hemoglobin was 60 per cent; red blood cells, 2,775,000; white blood cells, 6,750; polymorphonuclears, 76 per cent; lymphocytes, 20 per cent; monocytes, 4 per cent, and stool, negative. In the roentgenographic examination the views of the chest showed thickened pleura in the right axillary region and thickening of the interlobar pleura. The right leaf of the diaphragm was elevated and immobile with obliteration of the cardiophrenic angle in the posteroanterior view of the apex of a triangular bulging of the right diaphragm pointing toward the hilum of the lung (Figs. 14 and 15). Intratracheal lipiodol instillation revealed bronchohepatic fistula (Fig. 16).



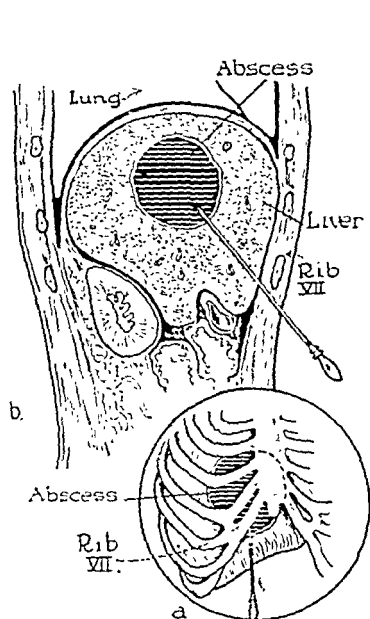


Fig. 22.

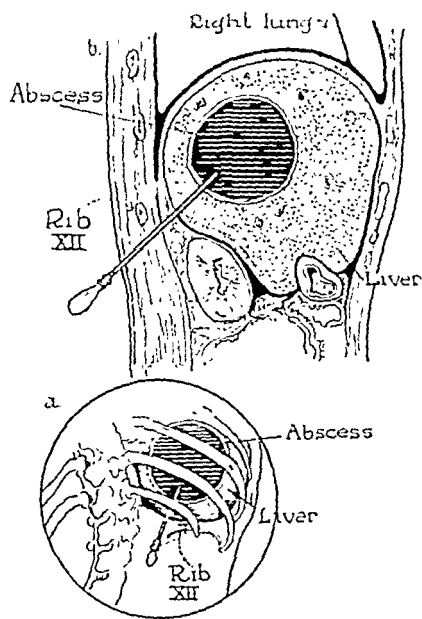


Fig. 23.

Fig. 22.—Technique of aspiration of amebic hepatic abscess located in anterior portion of liver. *a*, The needle is inserted just below the anterior costal margin about 4 to 6 cm. lateral to the midline. *b*, Diagrammatic representation of sagittal section at level of cutaneous puncture showing needle directed superiorly and posteriorly into abscess cavity.

Fig. 23.—Technique of aspiration of amebic hepatic abscess located in posterior portion of liver. *a*, The needle is inserted in the right lumbocostal angle. *b*, Diagrammatic representation of sagittal section at level of cutaneous puncture showing needle directed superiorly and anteriorly into abscess cavity.

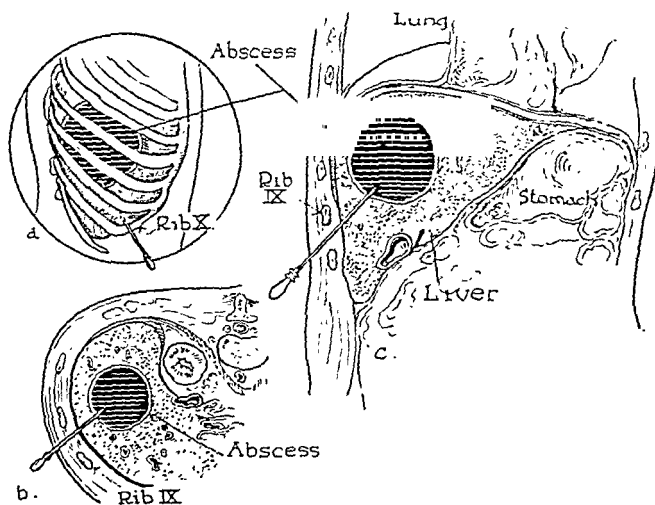


Fig. 24.—Technique of aspiration of amebic hepatic abscess located near dome of liver. *a*, The needle is inserted through the ninth or tenth intercostal space in the anterior axillary line. *b*, Composite diagrammatic representation of horizontal section through liver abscess and cutaneous puncture site showing posterior and medial direction of needle. *c*, Diagrammatic representation of sagittal section at level of cutaneous puncture showing superior direction of needle into abscess cavity.

lifting a crate of oranges. This forced him to quit working. He used turpentine as a "rub medicine" to the painful area. However, he obtained no relief and the pain began to extend higher up into his chest. It was especially aggravated on deep inspiration and he gradually developed slight dyspnea. He stated that one week before he experienced this sudden pain he had a "cold" in his right chest. He did not think he had much fever or chills. He had a cough for several weeks and began expectorating some mucopurulent material, sometimes brownish tinged. His appetite had not decreased very much but he lost about twenty-five pounds in one month. He was slightly constipated and had never had diarrhea for a prolonged period.



Fig. 20.

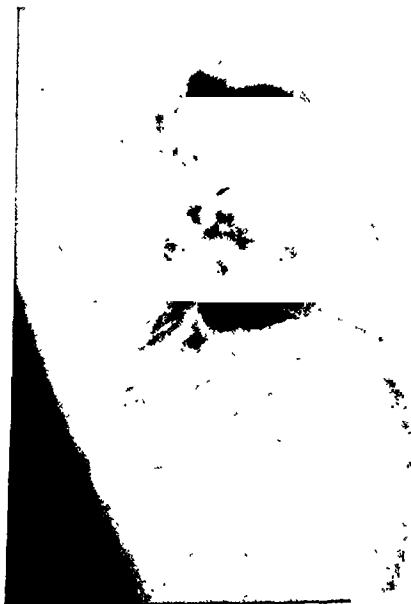


Fig. 21.

Fig. 20.—Lateral roentgenogram of the chest of the patient referred to in Figs. 18 and 19 taken after diagnostic thoracentesis which revealed chocolate-sauce pus. The fluid level may be clearly observed in the right pleural cavity.

Fig. 21.—Lateral view of the chest of the patient referred to in Figs. 18, 19, and 20 taken about one month after emetine and aspiration therapy. The right leaf of the diaphragm which is still somewhat elevated can now be delineated and the opacity in the chest has practically cleared. The patient was symptomless at this time and considered sufficiently recovered to be discharged.

*Physical Examination.*—Temperature was 99.4° F.; pulse, 120; respiration, 40; blood pressure, 100/70. The patient was a well-developed but somewhat poorly nourished colored male, lying quietly in bed apparently not acutely ill but having a slightly worried facies. Significant findings were limited to the chest and abdomen. There was a distinct lagging of the right side of the chest with increased tactile fremitus and dullness below the right second rib laterally and posteriorly. Resonance was definitely impaired on this side with almost absent breath sounds and a few fine râles. The heart seemed to be shifted to the left. Definite tenderness and rigidity were present in the right upper abdominal quadrant and the liver was palpable three fingerbreadths below the costal margin.

*Laboratory Findings.*—Hemoglobin was 65 per cent; red blood cells, 3,470,000; white blood cells, 17,000; polymorphonuclears, 73 per cent; lymphocytes, 18 per cent; monocytes, 9 per cent; blood chemistry, normal; urinalysis, negative; and Wassermann, negative. Bacteriologic examination of aspirated pleural fluid showed it to be

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sterile, and stool culture was negative for typhoid, paratyphoid, and bacillary dysentery. Stool examination revealed *E. histolytica* cysts. Sputum examination was negative for ameba and acid-fast organisms. Roentgenographic examination on Sept. 8, 1941, of anteroposterior and lateral views of the chest showed opacity of the right hemithorax in the lower two-thirds indicating presence of fluid in the right pleural cavity (Figs. 18 and 19). Roentgenograms taken after diagnostic thoracentesis revealed fluid level in the right pleural cavity (Fig. 20). Roentgenograms of the chest taken about one month after aspiration of chest and emetine therapy show opacity in the chest practically cleared with some elevation of the right leaf of the diaphragm (Fig. 21).

*Clinical Course.*—A tentative diagnosis of right bronchopneumonia with pleural effusion was made and the patient placed on sulfathiazole therapy for about five days. The temperature, which ranged around 99.6° F., gradually diminished slightly on sulfathiazole therapy but as soon as it was discontinued the temperature began to return to its former level. Following the demonstration of *E. histolytica* cysts in the stools and the aspiration of characteristic chocolate-sauce pus from the chest, the diagnosis was changed to amebic hepatic abscess with rupture into the pleural cavity and the patient was transferred to surgery. He was immediately placed on emetine therapy and another thoracentesis was performed with the removal of about 400 c.c. of typical chocolate-sauce pus. The temperature dropped to normal within 48 hours and remained there until his discharge. The clinical manifestations were also completely relieved.

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and accurate. Likewise, the classification of chronic cystic mastitis of the breast is not descriptive or consistent. The reviewer is well aware of the fact that there is no general agreement among authorities on the classification and even other features of chronic cystic mastitis.

In general the text is an admirable one, particularly for students. It reads so easily that all physicians should find it interesting. It is perhaps the best one in its field, and represents a fine addition to a medical library.

**The Hand: Its Disabilities and Diseases.** By C. W. Cutler, Jr, M.D., F.A.C.S., Associate Surgeon, Roosevelt Hospital, Director of Surgery, Welfare Hospital, New York City. Pp 372, with 274 illustrations. Philadelphia and London, 1942, W. B. Saunders Company.

This book is encyclopedic in character in that it is composed chiefly of a summary of the literature, with excellent illustrations from that literature on each of the subjects considered. There appears to be, therefore, very little information original with the author.

In one sense, the book is probably more extensive in coverage than necessary. It deals not only with the infections and ulcers peculiar to the hand, but also with many subjects in which consideration of the hand is only incidental, such as clubbing of the fingers in cardiorespiratory disease and the manner of taking of diverse types of skin grafts, omitting the Padgett dermatome.

On the credit side, there is good coverage of the subject of anatomy, infections, burns, wounds, fractures and dislocations, tumors, etc. There is a long list of references following each chapter, and the types of therapy outlined for the most part represent the ideas accepted by leading authorities such as Kanavel, Koch, etc.

Due to several excellent recent publications, there was no vacancy in the surgical literature requiring the preparation of this volume, but it is, nevertheless, an excellent book and one which has the advantage of presenting a wide review of the literature.

**Surgery of the Ambulatory Patient** By L. K. Ferguson. Pp 923, with 645 illustrations. Philadelphia, 1942, J. B. Lippincott Company. \$10.

The author has done a good job in a comprehensive review of many surgical conditions, but the choice of the title seems a bit unfortunate. Not all the patients that come with the diseases described are ambulatory nor are all of the treated patients ambulatory, whether they are in a hospital or not. Just what patients may be ambulatory is akin to what constitutes "major" and "minor" surgery. There is danger in a book of this sort of suggesting that certain surgical procedures are of minor importance. However, as the author stresses, there is no surgical procedure that should not have careful thought given to the details before, during, and after operation.

To be sure, some doctors misuse the time and money of a patient in prolonged and unnecessary hospital stays. Especially in these times of crowded hospitals, procedures that can be safely carried out in the office and do not incapacitate the patient certainly are in order. However, unless one has the facilities and assistance, it is hazardous to attempt to do even minor surgical procedures in the average doctor's office with questionably sterile equipment and inadequate facilities in case an emergency should arise. In the reviewer's opinion, procedures that can be carried out in the office are better carried out in an operating room of a hospital. Most hospitals, in this vicinity at least, charge no more for an operative tray in the operating room than they do in the receiving ward. Whether or not

## Book Reviews

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**Changes in the Knee Joint at Various Ages** By Granville A. Bennett, M.D., Associate Professor in Pathology, Harvard Medical School, Hans Waime, M.D., Resident Assistant in Medicine at Harvard Medical School, Walter Bauer, M.D., Associate Professor in Medicine, Harvard Medical School Pp 97, with 31 illustrations New York, 1942, Commonwealth Fund Publishers

A monograph of this sort has long been overdue. The material in this book serves as a base line from which to begin the study of pathologic material. The authors stress, particularly, the mechanistic conceptions of the origin of degenerative changes in the articular cartilage of the knee joint. There are a large number of fine plates upon which are exhibited photographs of the knee joint and microphotographs of the joint cartilage. Beginning as early as the second decade of life, and quite regularly in the fifth (after 40 years) gross evidence of degenerative changes in the articular cartilage is a regular finding. This wear and tear is a progressive phenomenon increasing in severity with added years.

This is a monograph deserving of careful study by all who profess an interest in the pathology of arthritis, be he pathologist, internist, or surgeon.

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**Surgical Pathology** By William Boyd, M.D., LL.D., M.R.C.P., Professor of Pathology, University of Toronto, Toronto. Ld 5 Cloth Pp 843, with 520 illustrations Philadelphia and London, 1942, W. B. Saunders Company \$10

The author has completely revised this edition and likewise has made numerous improvements in the illustrations. It is very gratifying to the reviewer to note that he discriminates sharply between the specialties of surgical pathology and pathology, he correctly calls attention to the fact that surgical pathology involves the study of disease processes in their incipency, whereas pathology is apt to be a study of the terminal phases of disease. However, he correctly states that a surgical pathologist should have preliminary training in pathology.

The author has adopted a clear, concise but simple style of writing. Because of this, the text lends itself very well to use by the student. The book is remarkably free from complicated discussions. The classification of tumors is simple and brief, to those trained in surgical pathology it might appear too brief but to the student, the reviewer believes, it is superior to a more inclusive classification. The author inserts sufficient material on pathogenesis and clinical manifestations to hold the reader's interest and lend proper correlation.

One of the many changes in this edition over the last one is the inclusion of carcinoma of the kidney and hypernephroma into one group namely Hypernephroma. This change in classification might be controversial, but is in expression of the author's opinion. In general the text material represents the author's experience but he refers constantly to the work of many other authorities to bring his material up to date.

Naturally, certain places are encountered which could be improved. The reviewer was disappointed in the author's classification of goiter. He had not adopted any consistency in the classification. Certainly the simple classification submitted years ago by the American Association for the Study of Goiter appears more descriptive.

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## Original Communications

### THE UTILIZATION OF ENCEPHALOMYOPEXY IN SELECTED CASES OF POST-TRAUMATIC FOCAL EPILEPSY

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*(From the Department of Neurological Surgery, Jewish Hospital of Brooklyn)*

EFFORTS to ameliorate epilepsy by augmenting the circulation of the cerebral cortex are not new. Among the earliest attempts were those of Alexander,<sup>1</sup> who tried to accomplish this result by cervical sympathectomy. Penfield<sup>2</sup> has called attention to a case in which "removal of the superior sympathetic ganglia, decortication of the carotid artery, removal of the ganglia upon the vertebral artery, and decortication of that artery" on one side converted a case of generalized epilepsy into unilateral epilepsy which continued for a year. This same investigator,<sup>3</sup> on the basis of his experiences at the operating table, concluded that "the one constant visible phenomenon in the brain during an epileptic seizure is cessation of arterial pulsation. The vasomotor spasms and changes seen so characteristically in the cerebral cortex of epileptics are due to vasomotor reflexes but reflexes which are probably not subserved by autonomic neurones placed outside of the cranial cavity." It would thus appear that the failure of cervical sympathectomy to effect a sustained improvement may be attributable to the fact that the resultant enhancement of the cortical circulation is not substantial or lasting. That this possibility is the case is also suggested by experiments disclosing that only slight cerebral vasoconstriction can be produced by cervical sympathetic stimulation.<sup>5</sup>

That a sustained revascularization of the brain is possible in lower animals has been proved by German and Taffel,<sup>6</sup> who accomplished this result by grafting a scarified muscle flap onto a brain surface denuded of its arachnoid investment, an application of the principle previously applied to the vascularization of organs other than the brain, notably the heart<sup>2</sup> and kidney.<sup>4</sup> Using monkeys as experimental animals they were able to demonstrate new patent anastomotic channels as early as three

a patient is ambulatory after certain operations will depend upon the temperament of the patient and the surgeon. The trouble with most "ambulatory" surgery is that too big a job is attempted without adequate assistance and facilities.

In the main, the subjects are discussed very well. If the author had attempted to discuss fewer surgical conditions, the book would be more valuable. After all, infections on the lip are not treated generally with the patient ambulatory; also, it is questionable if one is justified in allowing a patient with an abscess of the breast, who has a fever, to be ambulatory even though the abscess is drained.

The book is profusely illustrated. The illustrations are the best the reviewer has seen in a book of this type. A comprehensive index is appended.

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**Abdominal and Genito-Urinary Injuries.** Military Surgical Manuals, National Research Council. Pp. 243, with 28 illustrations. Philadelphia, 1942, W. B. Saunders Company.

This monograph written in two parts—one on abdominal injuries, the other injuries of the genitourinary tract—was prepared under the auspices of the Committee on Surgery of the Division of Medical Science of the National Research Council. Both portions of the volume are well done. The first section on Abdominal Injuries was written by Ambrose H. Stoick; the Urological Section was written by the Subcommittee on Urology of which Herman L. Krietschmer is chairman. The latter section contains a chapter of "Do's and Don't's" for the care of urological emergencies. The illustrations in both sections are well chosen and complement the text in a very satisfactory manner.

This volume should prove a very valuable compendium for medical officers of both the Army and Navy. It can be recommended enthusiastically, too, to anyone who wishes to inform himself on the best current thought of the management of abdominal and genitourinary injuries.

initially to a type of case in which severe convulsive manifestations were associated with a focal atrophic lesion. A case ultimately did present itself bearing criteria which were considered sufficient justification for operation, namely, a posttraumatic hemispheric atrophy with contralateral hemiparesis and jacksonian epilepsy involving the weakened limbs.

CASE 1 (Patient M. R.; J. H. B. No. 233773).—An 11-year-old girl was admitted to the hospital on Oct. 3, 1941, because of right-sided convulsions and paresis of the right limbs. She had fallen down a flight of stairs in June, 1937, following which a quadriplegia resulted. The weakness of the left limbs cleared up slowly, but there was a residual right hemiparesis.

Right-sided convulsions appeared two years following injury. They were frequently associated with unconsciousness, tongue biting, and loss of posture control. Before the institution of medication with phenobarbital, paroxysms occurred three or four times daily. On medicinal therapy their frequency was cut down to "once or twice a day several times a week." A pneumoencephalogram performed during hospitalization in June, 1940, established the diagnosis of left cerebral atrophy. The patient was readmitted in October, 1941, with a history of some progression in her right-sided weakness and a persistence of convulsions. The patient had been closely observed during 1941, but despite anticonvulsant medication, the widest intervals ever noted between attacks did not exceed three days.

The positive findings on neurologic examination included moderate facetiousness and mental retardation; slight awkwardness in speech without frank dysphasia; right spastic hemiparesis (about 40 to 50 per cent impairment), somewhat more marked in the upper limb; slight atrophy of the right limbs, hyperactive tendon reflexes on the right, absent abdominal reflexes, and Babinski toe sign bilaterally.

Preoperative electro-encephalographic studies disclosed "irregularities of pattern from all areas with concentration of disturbances (constant and spasmodic) anteriorly and to the left." (Rheinberger).

Operation.—A left lateral craniotomy and encephalomyopexy were carried out on Oct. 13, 1941, under general anesthesia. The exposed brain was found to be slightly atrophic and on palpation in the sylvian region to be fairly hard, suggesting the presence of a cicatrix.

Postoperatively, the patient fared well during the first twelve hours, after which she developed a series of right-sided convulsions, which cleared up within forty-eight hours. Thereafter, the patient was subject to relatively light convulsions, separated by steadily widening interparoxysmal intervals in place of the former more intense paroxysms occurring almost daily. Recently, seizures have been limited essentially to the right hand, although the right lower limb and the right side of the face are also involved occasionally. Paroxysms now occur at intervals of two to three weeks in place of the former maximal free interval of three days. The patient and family express satisfaction with the result, both as to epilepsy and motor weakness. While this has been apparent in the former, objective study could reveal no striking improvement in the latter.

Although the patient was appreciably improved following operation, the result secured was not as good as that seen in some of the other cases. In contrast to those in which convulsions did not recur, it is noteworthy that apart from the suggestion of atrophy the brain did not present a grossly abnormal appearance at operation. This fact and the electro-encephalographic evidence of diffuse bilateral dysrhythmia, pre- and postoperatively, suggest that this type of case is less suitable for encephalomyopexy.

weeks following operation. These investigators suggested the possibility of this procedure for such conditions obtaining in humans as "cerebral arteriosclerosis, recurrent cerebral thromboses, and intracranial aneurysms requiring internal carotid ligation."

The ability to enhance the circulation of the brain in lower animal forms naturally raises the question of the utilization of encephalomyopexy in the human subject. In view of the evidence of irreversibility of destruction of Betz cells, it appeared too sanguine to hope that hemiplegias based on more than mere physiologic interruption could be favorably influenced by such a procedure. But the possibilities for epilepsy would not be governed by such limitations if the hypothesis relative to an underlying capricious cerebral vascular mechanism were substantially correct. Under such circumstances efforts to improve the cortical vasculature would appear rational.

#### TECHNICAL CONSIDERATIONS

To effect actual vascular anastomosis between the cortex and overlying muscle in the absence of intracranial hypertension, intervening arachnoid must be eliminated. Rather than strip it from the brain and thereby invite unfavorable hemorrhage, it was deemed preferable to accomplish the same result by lightly cauterizing the superficial portions of some of the more prominent exposed convolutions. At such points, firm anastomosis with a superimposed muscle flap could then be expected to take place.

The technical problem of swinging a pedicle flap of temporal muscle onto the cortex, without leaving a sizable bony defect, is a relatively simple one. The scalp and muscle flaps are each reflected separately. The underlying bone area is then removed en bloc. When ready for closure one wires the bone flap in place after having made a small opening at its base. The size of this defect is just sufficient to allow for the entry of muscle without constricting its pedicle.

Although the temporal muscle is deprived of its usual attachment to the skull by this operation, masticatory function is not interfered with, nor is the act of mastication accompanied by any untoward effects upon the patient. The contour of the temporal region on the operated side is not visibly altered, since the bone defect is quite small and situated in the infratemporal zone.

#### SELECTION OF MATERIAL

Only patients whose convulsive manifestations were quite consistently focal, or related to a local lesion such as an injury or former infection, were selected for operation. Furthermore, these phenomena had to correlate with an abnormal intracranial focus, demonstrable by pneumocephalography and/or electro-encephalography. Operation was not performed, despite these criteria, if the seizures were adequately controlled with medication.

It seemed advisable that the projected procedure be restricted

only indication of a focal lesion was the slight pneumoencephalographic evidence of cerebral atrophy on the side where mastoiditis had formerly been present. Unlike those cases in which convulsions did not recur, the brain did not present a grossly abnormal appearance at operation.

**CASE 4** (Patient S. T.; J. H. B. No. 253273).—A 31-year-old man was admitted to the hospital on April 21, 1942, with a history of right-sided convulsions, associated with unconsciousness and tongue biting, during the previous year. Seizures were not materially influenced by medication. For a year prior to the development of these paroxysms the patient had been subject to vertiginous episodes manifested by a flushing sensation in the head, accompanied by a feeling of anxiety. He had been hospitalized in 1916, following a fall from a fire escape, which rendered him unconscious. X-ray study on that occasion revealed a fissure fracture of the left parietal and temporal bones.

The neurologic examination revealed no abnormal findings. The systemic examination was likewise negative except for the elicitation of a blood pressure of 160/100. Laboratory studies were not of particular significance, except for the presence of 1 plus albuminuria. X-rays of the skull disclosed an area of about 3.5 by 4.5 cm. in the left posterior temporal region, where the irregular calcium distribution suggested a local lesion not unlike chronic osteomyelitis. Pneumoencephalographic studies disclosed a normal looking ventriculosubarachnoid system. Electro-encephalography revealed "essentially normal activity except for intermittent disturbances arising from the left temporoparietal area." (Rheinberger).

**Operation.**—A left lateral craniotomy was performed on April 27, 1942, under avertin and local anesthesia. The brain appeared degenerated. Some meningocerebral adhesions and leptomeningeal cysts were present. After preliminary excision of the old fracture area and separation of the underlying adhesions, an encephalomyopexy was carried out.

The patient's postoperative convalescence was uneventful. Seizures have thus far not recurred.

The features in this case underlying the favorable result secured were similar to those of the other favorable cases, namely, strictly focal manifestations based on a grossly abnormal brain lesion.

**CASE 5** (Patient A. B.; J. H. B. No. 249181).—A 15-year-old boy was admitted to the hospital with a history of right-sided convulsive seizures of four years' duration. Efforts to control the paroxysms with anticonvulsant medication, including phenobarbital and dilantin, were unavailing, seizures continuing to occur at about weekly intervals, interspersed with more frequent episodes resembling petit mal.

Significant in the past history was a skull fracture at the age of 6. The patient at birth had been a breech presentation and was delivered following a difficult labor lasting three days. It was believed that he sustained an intracranial hemorrhage. The patient was subject to neonatal convulsions which cleared up after two years and did not recur until more recently. Weakness of the right limbs was first noted at about 6 months of age.

Positive features on neurologic examination included an obvious psychomotor retardation (psychometric study revealed an I.Q. of 63), a palpable bony deformity of the left temporal region, right central facial weakness, slight weakness and atrophy of the right limbs, right deep hyperreflexia, and hemihypesthesia.

Significant in the work-up were the pneumoencephalographic studies which disclosed a left lateral porencephaly in association with the old skull fracture and secondary skull changes.

**Operation.**—A left lateral craniotomy and encephalomyopexy were carried out on May 27, 1942, under general anesthesia. Multiple loculated leptomeningeal cysts

CASE 2 (Patient H. B.; J. H. B. No. 242057).—A 54-year-old man was admitted to the hospital on March 13, 1942, with a history of left-sided convulsions, involving the face and limbs, occurring every two to four weeks despite medication with dilantin and phenobarbital. Most of the seizures were associated with unconsciousness. In 1932, the patient had been operated upon for a subdural hematoma situated over the right cerebral hemisphere. Convulsions made their appearance about three months following operation. Pneumoencephalographic studies carried out in 1934 and again in 1938 suggested the possibility of meningeal adhesions and right hemispheric atrophy. A trephine opening subsequently made over the right temporal region revealed no evidence of a recurrent subdural hematoma, but disclosed meningocerebral adhesions.

The neurologic examination revealed a paucity of positive findings. These included moderate psychomotor retardation and generalized hyperactivity of the tendon reflexes, greater on the left than on the right.

*Operation.*—A secondary right lateral craniotomy and encephalomyopexy were carried out on March 19, 1942. The brain at operation was the site of multiple, pitted, scarred, and atrophic areas. Most were discolored yellow and in some regions were in the nature of leptomeningeal cysts, which were evacuated where possible. Meningocerebral adhesions were present in a few places; they were not excised.

Postoperatively, the patient had an essentially uneventful convalescence. Seizures have not recurred.

This patient had a gross focal lesion underlying his jacksonian seizures. The lesion itself was not treated directly, it being much too extensive to justify excision without hazarding paralysis. The freeing of meningocerebral adhesions did not seem sufficient to explain the subsequent relief, as they accounted for only a small part of the local pathology.

CASE 3 (Patient S. M.; J. H. B. No. 245916).—A man aged 29 years entered the hospital March 31, 1942, because of convulsive seizures of not quite three years' duration. Paroxysms were of a major, generalized character associated with urinary incontinence and tongue biting. There were no focal features to the attacks. Such seizures occurred as frequently as three to four times daily when medication was not being taken. With medication paroxysms averaged about two to three a week. They were interspersed with episodes of momentary unconsciousness occurring frequently in the course of the day.

Of interest in the past history was the development of a right-sided deafness and facial weakness following a mastoidectomy in childhood.

The neurologic examination apart from the old right-sided deafness and facial weakness, disclosed a generalized hyporeflexia, with reflex activity somewhat greater in the right limbs than in the left. Laboratory studies were without significance. Pneumoencephalography revealed a slight enlargement of the right lateral ventricle suggesting atrophy in the surrounding brain substance.

*Operation.*—A right lateral craniotomy with encephalomyopexy was carried out on April 10, 1942, under general anesthesia. The brain at operation did not appear unusual.

The patient was discharged two weeks following operation. Thereafter, seizures of a major, generalized character, without focal features, reappeared. They were less frequent and intense, and of shorter duration than formerly. In contrast to the former frequency of two to three times weekly, seizures did not occur more frequently than once a week.

This case could not be considered one of material improvement. In retrospect, it probably represented a poor selection, inasmuch as the



In this connection it is noteworthy that in the experimental animals of German and Taffel<sup>6</sup> "the grafts were solidly attached to the underlying brain by a vascular layer of fibroblasts which gradually assumed the characteristics of adult connective tissue cells." Nevertheless, it is perhaps significant that although the animals were observed for periods up to twenty months, convulsions were noted in only one case. They occurred in the contralateral face, neck, and arm four days following the application of a temporal muscle graft, a time at which neither collateral circulation nor appreciable scar formation were yet present. Autopsy of this animal revealed no apparent cause for the convulsions on gross examination. The paroxysms were attributed to excessive operative trauma rather than to the formation of a fibroglial scar.

It is thought that the beneficial effects thus far noted are attributable to enhancement of the cortical vasculature for reasons already alluded to. In the absence of actual visible musculoencephalic anastomosis such proof would have to await histologic or possibly angiographic studies. For the time being the possibility of its presence is based on the experimental data of German and Taffel<sup>6</sup> and knowledge of the accidental production of such anastomoses occasionally resulting from compound skull fractures. That the mere presence of the contiguous muscle flap has not introduced a fortuitous physicochemical factor is deducible from the studies of Block,<sup>3</sup> who reported on the transplantation of a wide variety of foreign bodies into the defect left by cicatricectomy. Paraffin, celluloid, muscle, fat, and fascia were all used to no avail. Not only did these fail to influence seizures, but they also failed to inhibit the reformation of scar tissue.

#### SUMMARY AND CONCLUSIONS

1. Reported herein is the treatment of five cases of focal epilepsy by encephalomyopexy.

2. The theoretic considerations upon which this procedure is based are discussed.

3. Of the five cases operated upon, three have not been subject to recurrence of seizures thus far. In the remaining two cases the frequency and intensity of the paroxysms have diminished only moderately. Those in which seizures did not recur shared the common denominator of focal manifestations corresponding to a gross posttraumatic cerebral lesion, of a cystic degenerative nature.

4. Two patients who had preoperative hemipareses corresponding to their cerebral lesions believed themselves to be stronger in the impaired limbs postoperatively. This was not borne out by objective study.

5. The data at hand do not, as yet, permit final conclusions as to the efficacy of this procedure in selected cases of focal epilepsy. They merely suggest that it may have some merit and indicate the advisability of continued study.

were found in the temporal region, associated with overlying thinning, scalloping, and lateral protusions of the temporal bone. The subarachnoid space was distended. The brain itself in this region was atrophic and discolored yellow. Some meningo-cerebral adhesions were present. A few of these were freed but no attempt at cicatricectomy was made. Some of the leptomeningeal cysts were evacuated. The area of deformity in the squamous temporal area, measuring about 3 by 2 by 2 cm., was removed.

The postoperative course was uneventful. The patient was discharged on the sixteenth postoperative day. Seizures have thus far not recurred. The slight weakness of the right limbs appears to be unchanged, although the patient believes them to be stronger than formerly.

As in the other cases where the results were favorable, there existed in this case the common denominator of strictly focal manifestations based on a grossly abnormal cerebral lesion.

#### COMMENT

Of the five cases operated upon, three have not been subject to recurrence of seizures during the period of followup thus far, five to seven months following operation. In the remaining two cases the frequency and intensity of the paroxysms have diminished appreciably, but it is uncertain whether this particular improvement is to be attributed to operation. The postoperative medication in all instances was maintained as close as possible to that which failed to control seizures preoperatively.

The operation was well tolerated in every instance. No resulting impairment of function was observed. Two patients who were hemiparetic prior to operation believed themselves to be stronger in the impaired limbs postoperatively. This was not borne out by objective study.

Of interest is the type of case which responded most favorably. Those in which seizures did not recur shared the common denominator of focal manifestations corresponding to a macroscopic post-traumatic cerebral lesion, such as cystic degeneration. In each instance the site of the lesion and its extent were such as not to justify surgical removal without the expectation of possible resultant impairment of function and appreciable reformation of scar tissue. The two cases in which convulsions recurred did not present comparable lesions at operation. In one the brain appeared normal. The pattern of the seizures, furthermore, was not focal. In the other, the external appearance suggested slight atrophy, and palpation indicated a possible intrinsic scar. Although the seizures in this case were of a focal pattern, repeated electroencephalographic studies indicated a diffuse dysrhythmia over both hemispheres.

The question naturally arises as to whether myopexy does not substitute one epileptogenic scar for another. It appears probable that the muscle graft, while it does encourage scar formation, carries with it sufficient circulation to differentiate it pathophysiologically from known atrophic epileptogenic lesions, which are not quite so vascular.

# THE CRANIAL SERIOGRAPH AND ITS UTILITY IN NEUROLOGIC RADIOLOGY FOR CEREBRAL ANGIOGRAPHY

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*(From the Institute of Neuropsychiatry)*

**I**N PREVIOUS publications I have described in detail the modern technique employed (or latterly used) for obtaining complete cerebral angiographies. Complete angiography consists of examinations of three roentgenograms—arteriography, phlebography of the first and phlebography of the second phase.

Until recently we have left the technique of taking complete cerebral angiography up to the judgment of the individual examiner. I, at the onset and for some time thereafter, have employed the "escamoteador" conceived by Professor E. Moniz, and without a doubt would have continued to employ it if I had remained at a permanent location or institution. Because of the large size of the escamoteador, its difficulty of transportation precluded its general use. The importance of taking three roentgenograms at intervals of one and one-half seconds between each after the moment of completing the injection, is paramount, because although in many cases the arteriography alone is adequate to establish the diagnosis, frequently phlebography of the first phase or phlebography of the second phase is indispensable to establish an absolute diagnosis as we will see subsequently.

I wish to emphasize again the fact that with a single injection of a radiopaque substance (thorium dioxide or diodrast) it is possible to obtain the three aforementioned plates using our technique and our cranial seriograph. Unfortunately, people still do an incomplete angiographic exploration. In a recent publication of Gross<sup>1</sup> still only arteriography is mentioned.

The model of the "seriograph," which we have been using these past few years and which will be described later, has as its principal characteristics a portable size adaptable to any x-ray table, and a smooth and certain function. This model for cranial angiograms has provided ample proof of its utility, maneuverability, ease of function, and portability during the past five years which I have emphasized in the several clinics in which I have worked recently. The cranial seriograph is constructed to be used with 10 by 12 x-ray film and is made up as a box 15 by 12½ by 4 inches, the inside of which contains vertical springs of steel and a platform of two horizontal frames which articulate at four points, the latter moving freely on the bottom of the case by a system of rounded edges. On this platform are placed three identical trays (cassette carriers) measuring twelve and seven-eighths and fourteen and two-eighth inches, inside of which are placed thin sheets of lead.

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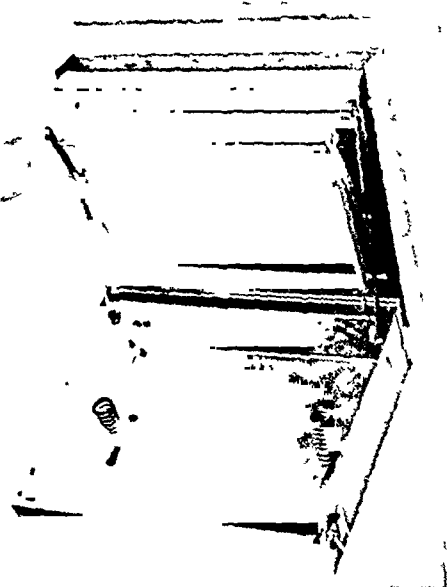


Fig. 2.



Fig. 3.

Fig. 2.—The cranial seriograph showing the combination of springs and cross arms with rollers which provide steady, precise, smooth function.

Fig. 3.—The cranial seriograph loaded and just prior to being closed and placed on the x-ray table. Observe how the trays and cassettes are in perfect equilibrium. The cover can be closed easily without requiring compression.



Fig. 4.—The seriograph loaded and in position on the x-ray table, with the tube centered and also the lead protector which prevents the exposed films from further exposure to x-rays.

The cassettes are placed over the lead sheets, which should be equipped with reinforced metallic edges.

As the external measurements of the cassette 10 by 12, which are preferred for these purposes, vary according to the particular commercial source, our cranial seriography can be used with any standard cassette, provided there are employed as needed small strips of wood of various sizes to provide immobility of the cassettes in the tray.

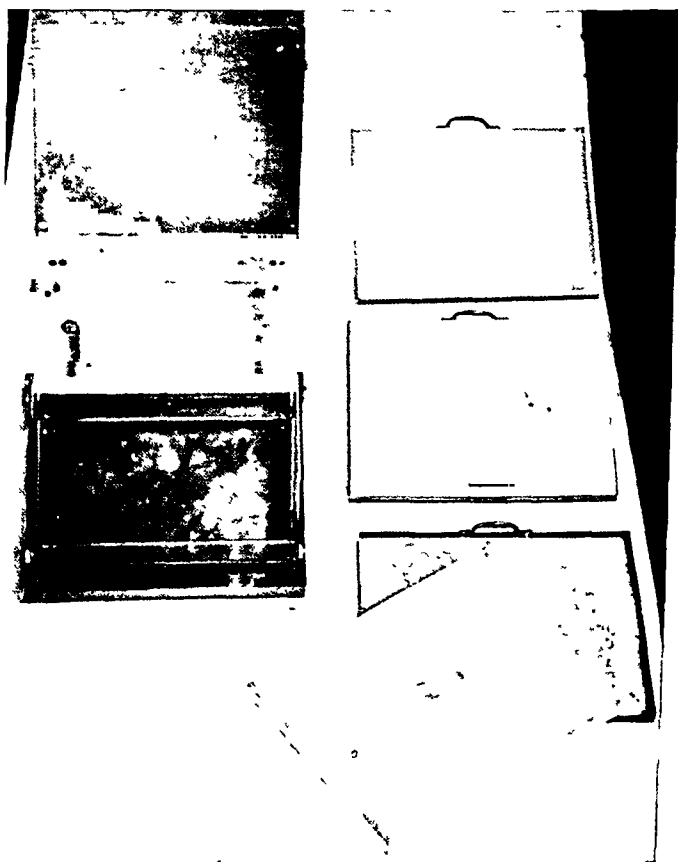


FIG. 1.—The cranial seriograph, showing all the different parts of which it is constructed. The cover is formed by a Lysholm grid. The box shows the vertical springs. The movable platform shows the horizontal springs and articulated arms. The tray and cassettes are in position.

The cover of the box has on its superior surface a Lysholm grid protected within by an aluminum plate of the same dimensions. The vertical springs are two inches in height but no longer function when tray No. 1 and its cassette flip out, while the horizontal frames remain functioning, due to the articulated lever, and act on the second and third cassettes. The power of the springs and their action are adjusted in such a form to permit equilibrium and a constant balance between the individual trays with their cassettes, even when they are slipped out one by one.

The cranial seriograph is placed at the extreme end of the x-ray

center of the seriograph, which corresponds with the center of the film. Once this has been done the patient is placed on the table in the supine decubitus position and the patient's head rested on the cranial serialograph so that the side of the head is on the instrument. It is advisable to place a pillow under the shoulder on the side one desires to use for the injection. This facilitates securing the posture sought. A band maintains the head in position. After exposing the common carotid, the injection of 6 c.c. of the radiopaque substance is made (diodrast or thorium dioxide) and at the same instant this has been completed, the initial film is exposed for 0.2 second. This is the arteriogram. The No. 1 tray and its cassette are then slipped out, and remain protected



Fig. 7—Cerebral tumor of posterior part of parietal lobe. In this case the phlebogram of first phase (second film of the complete angiogram) was necessary to establish the diagnosis. The arteriogram and the phlebogram of the second phase had a normal appearance

by the lead box. After one and one-half seconds have elapsed, the second film is exposed for 0.2 second. This is a phlebogram of the first phase. The No. 2 tray and its cassette is then removed and comes to lie over the No. 1 under the lead protector. After an elapse of an additional one and one-half seconds, the third exposure is taken. This is the phlebogram of the second phase. The third tray is then removed, all are developed, and one has the complete angiogram.

In order to complete this work, I will present three cases which illustrate clearly the necessity of employing complete cerebral angiography in order to obtain a complete exploration.

In the first case one can observe the lesion in the arteriogram phase, the first plate of the complete angiogram. It is a tremendous aneurysm

table and equidistant from each edge, loaded with three cassettes. The end of the apparatus for receiving each exposed cassette is protected by a lead covering as depicted in Figs. 4 and 5. The x-ray tube is centered at a distance of forty inches so that the central rays pass through the



Fig. 5.—Panoramic view of cranial seriograph in position with the tube adjusted and ready for use



Fig. 6.—Aneurysm of internal carotid. In this case, arteriography (first film of the complete angiogram) was sufficient to establish the diagnosis. The phlebograms of first and second phase had a normal appearance.



## THE SUPPRESSION OF INFECTION IN RECENT WOUNDS BY THE USE OF ANTISEPTICS

THOMAS BEATH, M.D., F.R.C.S. (ENG.), RICHMOND, VA.

*(From the Department of Surgery of the Medical College of Virginia)*

I AM well aware that there is a strong group of surgeons who feel that no antiseptic should be used in recent wounds and I understand that this view is held by them because they consider that no antiseptic will kill all the bacteria in a wound and that if any antiseptic is used it will so damage the tissues of the wound that the natural body defense is less able to cope with the remaining organisms than if the antiseptic were not used. In order to refute at once the existence of a general law that bacteria cannot be critically damaged by chemicals without damaging the tissues more, I would point out that the sulfonamides so damage bacteria that they cannot feed themselves and reproduce and are thus rendered an easy prey for the attacking antibacterial forces of the tissues, and penicillin appears to be both bactericidal and harmless to tissues in bactericidal strengths. These examples make it obvious that it is not necessarily hopeless to find a chemical which will damage or destroy bacteria in a wound and still leave the tissues essentially unharmed.

Because there are new antiseptics being offered by the drug houses it seemed desirable to inquire whether any of them presented qualities which would make them more likely to be useful in suppressing infection in wounds than the antiseptics which many surgeons have decided are useless. In war this problem seems particularly important.

An antiseptic to be effective for our purpose should probably possess the following capabilities:

1. In the strength used it should kill germs if diluted at least two to four times more.
2. It should retain most of its germicidal ability in the presence of serum, blood, and crushed tissue, as well as miscellaneous dirt.
3. The essential chemical should not react with the tissue juices or blood and thereby be rendered inert.
4. It should not be a protein coagulant like phenol because on application a scum of coagulum might bridge over microscopic pockets and prevent the deeper penetration of the antiseptic.
5. It should interfere to a minimum with the power of the blood by its leucocytes and the tissues to deal with organisms not killed by the antiseptic.

of the internal carotid. The phlebograms of the first and second phases were normal.

In the second case the angiogram shows an arteriogram difficult to interpret but the phlebogram of the first phase (the second film of the complete angiogram) shows very clearly a shadow corresponding to a cerebral tumor of metastatic carcinoma type, a fact corroborated by



Fig. 8—Parietal meningioma of the right side. In this case the phlebogram of second phase (third film of complete angiogram) was indispensable to the establishment of the diagnosis. The arteriogram and phlebogram of the first phase were less demonstrative.

necropsy following an operation. This tumor corresponded in size with the one shown in the phlebogram of the first phase. The phlebogram of second phase was essentially normal. The final one of the three cases was one seen on the University neurological service. It was a meningioma. The arteriogram and phlebogram of first phase were both essentially normal, but the phlebogram of the second phase (third film of the complete angiogram) shows very clearly the existence of a very vascular meningeal tumor.

I believe that these cases are sufficiently eloquent to emphasize the importance of obtaining the three phases of cerebral circulation with a single injection of 6 c.c. of radiopaque substance (diodrast or thorium dioxide) and to accomplish by this method a complete angiographic exploration.

Our seriograph makes this object possible and simple.

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3. The essential chemical should not react with the tissue juices or blood and thereby be rendered inert.
4. It should not be a protein coagulant like phenol because on application a scum of coagulum might bridge over microscopic pockets and prevent the deeper penetration of the antiseptic.
5. It should interfere to a minimum with the power of the blood by its leucocytes and the tissues to deal with organisms not killed by the antiseptic.

6. It would be desirable if the antiseptic could cross cell membranes and kill organisms which had somewhat invaded the tissues. It seems probable that no antiseptic has this power to a useful degree.

7. It should be nonselective toward various bacteria. All the antiseptics to be considered are fairly nonselective but the coal tar derivatives, dettol and amphyl, like phenol show minimum selectivity.

8. The product should be sufficiently inexpensive that one will feel no hesitation in using as much as desired.

9. It should be of proved clinical value.

The following antiseptics were inquired into to see how well they fulfilled the above requirements. (A summary of the study of the literature is here presented, a more complete review of which is given elsewhere.<sup>1</sup>) They are: 1 per cent aqueous iodine (Lugol's solution diluted 5 times), 5 per cent dettol (Dett),  $\frac{1}{2}$  per cent amphyl, 1/500 metaphen, 1/3000 furmerane, 1/1000 zephiran, 1/1000 merthiolate, 1/1000 proflavine (and acriflavine and 2:7 diaminoacridine hydrochloride).

The order in which these were named represents roughly their germicidal power in terms of which can be diluted more and still kill bacteria. It is probable that none kill spores in the time they could practically be used in treating a wound. The available data make it impossible to place furmerane, zephiran, metaphen, and merthiolate with exactness.

I shall now consider each of these individually. Since my conclusion is that iodine, furmerane, zephiran, metaphen, and merthiolate do not seem to hold much hope I shall discuss them first.

*Iodine 1 per cent* (Lugol's solution diluted 5 times) is a powerful germicide in an aqueous medium and can kill germs if diluted about fifty times. However, it combines rather freely with almost any organic material and is largely inactivated by blood. It coagulates proteins and four times greater strength is necessary to kill bacteria than leucocytes in the presence of fifty per cent blood. It is therefore not likely to be a useful antiseptic.

*Merthiolate, Metaphen, and Furmerane* are organic mercurials and though furmerane has just recently been released\* and there is as yet little information available about it, it seems proper to group it with the other two.

In a general way the germicidal activity of the solutions of merthiolate and furmerane recommended for use are about equal while that of metaphen is somewhat greater. Generously regarded, the mercurials can be diluted five to ten times and kill *Staphylococcus aureus* in ten minutes. In passing, mercurochrome "can be condemned on the ground of deficient bactericidal powers alone."<sup>2</sup>

\*Released by G. D. Searle & Co., Chicago, Ill.

The mercurials in other ways fall down seriously. They are largely inactivated by the presence of blood and serum. They appear to be highly toxic to tissues and especially to leucocytes. This great tissue toxicity nullifies any values they may have as bacteriostatic agents for the mere temporary checking of growth is of minimum value because if live leucocytes are not promptly forthcoming the organisms soon begin to grow again.

The mercurials then would seem to be unreliable for this purpose.

*Zephiran* is a nonmercurial antiseptic of somewhat greater germicidal power than merthiolate and metaphen when organic material is absent. It appears to be subject to the same disadvantages as the mercurials. Its potency is tremendously decreased by the presence of blood or serum. It precipitates with serum or laked blood and is the only one which does. It is toxic to leucocytes if diluted to 1/100,000 (i.e. the 1/1000 solution diluted 100 times). It therefore seems that it would be unreliable for our purpose.

*Dettol 5 per cent* (Dett) is made by diluting to one to twenty dettol as supplied by the manufacturer.\* In a 5 per cent solution it has strong germicidal power (i.e. somewhat greater than the mercurials) and this is only moderately decreased by the presence of large amounts of organic matter. The essential chemical is not dissipated by combining with tissue proteins. It does not precipitate proteins. It is almost wholly nontoxic to fixed tissues but is probably toxic to leucocytes. A wound can be soaked for an hour without grossly damaging the tissue. The material is a solution of a synthetically modified cresol. It would seem to be worth considering the use of 5 per cent dettol for application to wounds.

*Amphyl† ½ per cent* is a product which is somewhat similar to dettol but has an added ingredient. It is recommended by the maker that it be used in ½ per cent strength and this has less reserve germicidal power than 5 per cent dettol. Until information is available that it can be used successfully in less dilution than ½ per cent strength and until more is known of the toxicity to tissues the 5 per cent dettol should be the preferred product. Amphyl may later, however, be shown to be the equal or superior product and is worth watching.

*Acridines* (Proflavine, 2:7 diaminoacridine hydrochloride) are more familiarly known as flavines and the best known is acriflavine. Used in 1/1000 solution these chemicals are slow but sure germicides with the ability, about equal to the mercurials, to kill organisms on further dilution if given time for their action. They are bacteriostatic in much weaker dilutions than they are quickly bactericidal. While they do not completely sterilize a culture of organisms quickly, they tremendously reduce the bacterial population in reasonable time and appear to decrease the virulence of the unkilld bacteria, making them more

\*It is obtained from Reckitt and Colman Canada Limited, Montreal, or Atlantis Sales Corp., Mustard Street, Rochester, N. Y.

†Offered by Lehn & Fink of Bloomfield, N. J.

susceptible to attack by leucocytes. This point about the bacteriostatic action may be an important difference from that of the mercurials. The germicidal power is not materially influenced by the presence of serum or whole blood. Proflavine and 2:7 diaminoacridine appear to be no more toxic to tissue than normal saline solution, while acriflavine is somewhat toxic. Weak but bactericidal strengths interfere to a minimum degree with the activity of the leucocytes. The flavines have been shown to be of some definite value in preventing infection in experimental wounds in laboratory animals. As acriflavine is slightly more toxic than proflavine and as 2:7 diaminoacridine does not seem to be available in this country, among the flavines proflavine is the one of choice.

#### SUMMARY

Laboratory considerations would lead to the choice of 5 per cent dettol (Dett) or proflavine sulfate 1/1000 as being antiseptics with some hope of them being useful in suppressing the development of infection in wounds. Dettol (Dett) is a rapid acting germicide not grossly toxic to tissue but probably toxic to leucocytes, while proflavine is a slow acting germicide with great bacteriostatic powers and essentially non-toxic to tissues.

Being unable to find clinical reports in which these substances were given a chance to be effective, I began a clinical experiment to test them out. Lacerations of the hand have the features that: it is particularly desirable to get healing by first intention; they may require burying of suture material to suture tendons or nerves; the amount of soiled tissue which can be sacrificed by débridement is limited, and the blood supply of some of the remaining tissues may be poor. I therefore felt that wounds of the hand would be particularly suitable clinical material for a test. The completed test is to consist in soaking wounded hands in dettol or proflavine for three-fourths hour with the precaution that gross dirt and blood clot are removed and that the antiseptic reaches all parts of the wound. In practice I infiltrate the tissues around the wound putting the needle through sterilized clean skin at a distance from the wound edge, apply a tourniquet to the forearm to completely close the arteries, clip the fingernails short, wash the wound completely free of blood clot and macroscopic dirt using a sterilized brush and dettol solution, then soak the part for forty-five minutes and suture the wound. No débridement is done except where obviously nonviable tissue is present. If the patient does not tolerate the tourniquet well I remove it at about half time and reapply it. I usually scrub out the clot which accumulates from venous oozing two to three times during the soak. So far I have not tried the proflavine; the first cases with dettol were done in August, 1941.\*

\*I do not expect to be able to complete the experiment in the near future, therefore I felt that the results shown by a limited number of cases should be presented in the hope of interesting others in the matter.

Some hand injuries have not been treated by me in this experiment for I have felt that they were of no use in determining the value or the lack of value of the antiseptic method. The cases which were not accepted as test cases are:

1. Those in which the wound could not be closed, i.e., cases with loss of skin in which surgical judgment indicated that healing by granulation should be allowed. In such cases I could see no way to tell whether the antiseptic was of any value.

2. Superficial wounds which required no suturing. Here there is no question of locking bacteria in the depths and thus the injury is not one in which a judgment could be formed.

3. Puncture wounds. Our antiseptic could not possibly penetrate in these cases and thus if the case healed without infection no credit could be given and if it did not heal no discredit could be given. I have accepted, however, all (which total only a few) of the deep penetrating wounds which had a narrow mouth. The mouth in these tended to close and I had to hold it open during the soak by loose gauze packing. There is some experimental evidence available supporting the contention that the potential infection of puncture wounds can be favorably influenced by infiltration of the track of the wound and surrounding tissues with some of the acridine antiseptics (proflavine, acriflavine, or trypaflavine). I have not, however, observed any of these cases.

The severity of the case has been no bar to their acceptance; in fact, the cases in the series are, on the whole, a little more severe than the average emergency room case requiring suture, for every now and then I would find a case which required suture for which I had not been called and find that the reason I had not been called was that the intern did not think it was a very serious case.

All but three of the cases were treated in the emergency room. It seemed impractical to insist on the elaborate technique of caps, masks, and gowns during the handling of these cases and I am inclined to think that the antiseptic clinging to the cut surface of the wounds is able to deal with any droplet infection which may occur. On this point I feel that these cases have been handled with somewhat less expense in operating room equipment than are those for which a more elaborate operating room set up is maintained. One of our emergency rooms is well equipped while the other, for colored patients, is crowded and poorly equipped. In the summer time in this one we keep a fan blowing on the operating field to keep the flies off! About two-thirds of the patients were treated by interns; some were interested and tried to carry out instructions carefully, some were the opposite.

In all there have been 100 cases. Eighty-six of these wounds healed by primary union in the most rigid sense. By this I mean that there was no pus whatever associated with the wound, there was no redness

or induration of the marginal skin, no soreness and no bead of pus associated with the stitch holes. One more case was wholly as successful except that a little redness occurred in the marginal skin which lasted a few days and then uneventfully subsided. In three cases a bead of pus oozed from one or two stitch holes on removal of the sutures and one of these three had a separation of the wound one-fourth inch long extending through the thickness of the skin but not deeper and the separation healed promptly (this case was not treated until more than twelve hours after the injury and no tourniquet was used). In one case the healing was equally successful except that a silk suture which had been used to suture the flexor tendon of the finger at the terminal interphalangeal joint worked itself out a year after the primary treatment. In two other cases, both of which involved jagged lacerations into the terminal interphalangeal joint, a small amount of pus lay between raised cornified epithelium and the deeper epithelium in the area of one part of the wound. This was found when the wound was dressed for the first time several days after the injury. The deeper part of the wound was healed and after the surface epithelium was trimmed away no further complications occurred in the cases. I am interpreting the situation in these cases as follows: that a blister of serum collected under the cornified epithelium which became infected through the stitch holes after the deeper part of the wound had become effectively sealed off. No deep suppuration occurred and since these wounds opened into the joint it would certainly not be missed if it had occurred. Good movement in the joint in both cases was developing rapidly when last seen. In one other case which required suture five wounds had been inflicted by contact with a powerful electric fan; one-half inch length of one of the wounds gaped open to a depth a little greater than the thickness of the skin on removal of the sutures; this promptly healed by second intention and as this was part of a wound which formed a flap of skin and as no inflammation or pus formation occurred under the flap and there was no inflammation or pus formation at the gaping portion until some days after removal of the sutures it seems likely that infection had been successfully controlled in the case but there remains the question of whether the antiseptic had had some deleterious effect on the healing process. If these eight cases are to be considered as successful from the point of view of prevention of infection—and I think they ought to be so considered—there remains only 6 cases out of the 100 in which infection occurred. None of these cases should necessarily be considered as failures, however, for the treatment planned was not adequately given in essential features. It is even questionable whether they should be included in the series but in the interest of accurate reporting I decided before the treatment was given and the result known whether to include a case in the series or not. To be convincing on the point of whether adequate treatment was given I shall present the following six cases in more detail:



CASE 1.—C. S., in the ninth case in the series, was treated Aug. 27, 1941. The tip of the middle finger had been crushed between the street curb and a heavy wheel. The pulp of the finger was burst on each side. The wounds extended on each side to very near the nail edge. The nail was long and considerable gross dirt was under it. The finger was soaked in the solution for forty-five minutes and the wound sutured. The nail was not clipped short and the gross dirt was not removed from the finger. I am told that a bursting injury of the pulp such as this will show, if examined, that the surface wound communicates by a continuous track of torn tissue with the depths of the pulp. It is not hard for me to imagine that a suction may have followed the bursting which could have sucked bacteria deeply enough into the wound to be beyond the depth of penetration of the antiseptic. Furthermore, with gross dirt left under the fingernail and around the nail it would not be surprising if some were picked up on the suture material, thus contaminating the wound during suturing. (No one expects antiseptics to consistently penetrate gross dirt and kill bacteria in the center of clumps.) The inflammatory process took three days to develop and was never severe.

CASE 2.—T. D., in the fourteenth case in the series, was treated Aug. 28, 1941. There was a jagged nail tear in the left hypothenar area. It was inflicted during a fall while a house was being demolished. The man, during the fall, tried to catch a beam and in doing so caught his hand on the old nail. Penetration was deep and the wound margin tended to fall together. No infections had been seen when this patient came for treatment and I took chances that I ought not to have and which I had specifically planned not to take. This injury was treated by simply immersing the hand in the bath and then suturing the wound. The error in this case was that arrangements were not made for the antiseptic to penetrate to the depths of the wound. I should have applied a tourniquet; then thoroughly removed the blood clot to the furthest depth to which the nail had gone; I should have visualized the pocket and should have seen to it that it did not refill with blood clot. (Looking back I can see that it was absurd to have expected the antiseptic to penetrate anywhere near to the bottom of the laceration in this case and I therefore feel that it should be excluded as a test case.) The infection was not a severe one but was severe enough to require wide opening of the wound.

CASE 3.—A. W. H., in the twenty-ninth case in the series, was treated Oct. 5, 1941. This wound was not soaked for as long a time as usual. It was a laceration one inch long, through the skin on the dorsum of the web of the right hand. The man was in a fight and hit a negro on the face; he thinks his hand hit a tooth. (I did not know the cause of the injury till after the treatment.) There was some tendency to the formation of a flap of skin. Antiseptic solution was squirted over the wound with an asepto syringe for fifteen to eighteen minutes (instead of the forty-five minutes usually used for soaking). A little oozing of blood was occurring and no effort was made to control it. The case subsequently was taken over by another physician who told me that he had to remove a stitch or two but that there was no other trouble and that healing was prompt. Whether a more successful outcome would have been obtained by a more prolonged and more efficient exposure to the antiseptic I cannot say.

CASE 4.—C. S., in the sixty-second case in the series, was treated Jan. 15, 1942. The wound was an inch long, cut by an axe into the extensor side of the metacarpophalangeal joint of the left index finger. The extensor tendon was completely divided and an opening of about one-fourth inch length extended into the joint. There was moderate oozing of blood. I discussed the treatment with one of our interns who had not used dettol before. I asked him to apply a tourniquet on the forearm, to clean out the blood clots with a scrubbing brush, to soak the hand for about five minutes, to irrigate the joint with the fluid for about twenty minutes,

and then further soak the hand for twenty minutes and suture the tendon and skin. I found out later however that he relegated the job to someone else, that a tourniquet was not used (and this seems essential), and that the irrigation into the joint was done for about one and one-fourth minutes (and I am not sure that the joint was properly irrigated for this is not easy to do through a small opening and the rest of the care given appears to have been slothful).

The sutures were removed on the eleventh day and there was no redness, swelling, pain or other evidence of infection. On the twenty-third day, however, the injured joint became sore and on the twenty-sixth day (Feb. 10) pus was oozing out from the joint, with a moderately acute inflammatory process going on. (I note in reports of experiments with laboratory animals that where antiseptics are not completely effective they may delay and minimize the infectious process.)

CASE 5.—S. T., in the ninety-second case in the series, was treated July 14, 1942. An inmate of city jail (because she refused antisyphilitic treatment) cut the palm of her left hand on a broken soft drink bottle. Tendons of two fingers were cut through a skin wound about three-fourths inch long. The case was treated wholly by the interns without supervision. A tourniquet was applied, procaine infiltration of the tissues around the wound was done, and the wound scrubbed out. After soaking for three-fourths of an hour the wound was enlarged proximally to reach the tendons and the suturing done. It is to be pointed out, however, that a wound in the palm, cut with glass deeply enough to sever tendons as in this case and still have a skin opening only three-fourths inch long, is very liable to have the characteristics of a puncture wound in some parts of its depth thus making special care necessary to remove deeply buried bits of blood clot (to allow access of the antiseptic to the depths) and to spread the wound open to allow access of the solution to the depths. In this case a more efficient access of the antiseptic would probably have been obtained by enlarging the wound before soaking rather than after and by suturing the tendons after about twenty minutes' soaking and then continuing another twenty to twenty-five minutes after completion of the tendon suturing, for then the retracted cut ends of the tendon (which must be to a degree contaminated by the injury) are brought down into contact with the antiseptic. Of course, any case with lacerated retracted tendons has to a degree the same difficulties as a puncture wound in having some pockets of the wound inaccessible to the antiseptic.

CASE 6.—A. W., a colored child, aged 8 years, in the one-hundredth case of the series, was treated Sept. 5, 1942. Glass cut the tendons of two fingers in the palm through a skin wound one-half inch long. The motions of the soaking treatment were carried out, namely a tourniquet was used and blood clot was removed from the wound by the use of gauze in forceps but without the use of local anesthetic. The hand was soaked and the suturing carried out. Sulfonamides were used in the wound and given by mouth. I knew nothing of the case until a week after the injury. Infection became evident about the eighth day. This case is similar to Case 5 with a greater degree of the inherent difficulties and errors of treatment. The blood clot could not possibly be removed by the method used in a child of this age and with a deep narrow-mouthed wound such as this without using local anesthetic and without opening the wound; the complication of the presence of blood clot during the soak introduces a factor which really nullifies the case as a test case. If this injury had healed without infection it would not have been included in the series because of having been treated with sulfonamides and statistically I may be wrong in including it.

Four untraceable cases were treated and are not included in the series. Some injuries in which it would seem to be very difficult to eliminate infection were treated. In some a considerable amount of silk was buried

subcutaneously. A fair number had opened joints. One was a compound fracture, caused by a saw cut through the back of the finger, the finger was attached only by the flexor tendons, vessels and skin; it was sutured back and recovery took place with no infection. When the patient was last seen he seemed to be developing a useful finger. In one case there was a volar flap of skin turned up over the crushed finger tip, the flap was so damaged that it died of dry gangrene but there was no infection or pus associated with it even up to two and one-half weeks when the sutures were removed; the margins of the shrinking flap were stuck by serum to the stump of the finger for the whole time and no pus was present under the dead flap when it was removed.

Eleven compound fractures of the large bones of the limb were treated by the use of the solution (not necessarily soaking). As far as judgment can be based on these I was impressed that the solution has been of help in suppressing infection. Five of them are old enough to indicate that the use of the solution does not interfere with bone healing.

In summary, I present 94 cases treated by this method with 94 primary unions but eight of which had a trivial infection. Six other cases were treated which developed infection but these were not correctly treated in the manner essential to allow efficient access and action of the antiseptic.

A simple attempt was made to get some idea of the bacterial flora in the wounds before and after soaking. For this a small piece of the wound surface (not skin) was put into broth before and after. Eighteen satisfactory before and after cultures were made. All showed growth when taken before the soak. Seven showed no growth after the soak. In some cases two organisms grew before the soak and only one after and in many of the cases which showed growth after, the growth did not come up for several days. *Staphylococcus* was by far the commonest pathogen and ordinarily it grows up in culture in twenty-four hours.

It is recognized that during the removal of blood clot and debris there is a mechanical removal of bacteria and that this is probably a factor in suppressing infection. I have been unable to devise a legitimate clinical experiment to eliminate this factor.

The purpose of this study was not primarily to develop a method of treating wounds of the hand but to try to find out if antiseptics are of value in suppressing infection of wounds. For this purpose it would seem logical to make wounds in animals and apply various bacteria followed by various antiseptics. This, however, has been amply performed and a summary up to 1922 is given by Neufeld.<sup>2</sup> There is ample proof in this of the value of antiseptics as far as animal experiments go.

I feel that I offer (1) strong reason to suppose that properly chosen antiseptics are of value in suppressing infection in wounds (2) a safe practical method of managing wounds of the hand. I do not say that

the antiseptic used is the best possible and I do not say that the method of application is the most convenient or most efficient possible. By the solution of technical problems it might be possible to make the method of prolonged soaking applicable and of some value in large wounds of other parts of the body. I suspect that those who believe antiseptics are of no value have based their judgment on the observed effects in wounds in which the antiseptic could not be expected to penetrate to all the implanted organisms, e.g., wounds of the last war, or on the observed effects of antiseptics which from laboratory considerations alone would not be expected to suppress the development of infection or on the observed results of clinical trials where the antiseptics were not given a contact with the wound for a sufficient duration of time. I do not wish it to be thought that antiseptics can supplant the removal of gross dirt from a wound or the judicious removal of nonviable tissue. They may supplement such procedures and the sulfonamide drugs may supplement both. It seems to me to be of great importance in any clinical trial that (1) gross dirt and blood clot be removed, and this usually requires a local anesthetic and sterile scrub brush, (2) that bleeding be stopped if possible, because blood clots get into the wound and prevent penetration of the antiseptic, (3) that no pockets are left into which there may be doubt as to the penetration of the antiseptic.

I would ask those who feel firmly that no antiseptic can be of value in suppressing wound infection to note that many injuries occur in factories where a first-aid station is available and that if these wounds were soaked for a little while in a suitable antiseptic and then a compress soaked in the antiseptic were applied for transportation, then the growth of bacteria in the wound would be somewhat checked and the numbers of bacteria in the wound to be dealt with at the final cleansing would surely be much less than otherwise and the hope of primary healing would be correspondingly increased. This would be especially true if the lag period of a couple of hours that bacteria take before growth gets underway is to be passed before the final cleansing is done.

*Relative Costs per Gallon Wholesale* (128 oz. per gallon = 3.63 litres).  
 —Zephiran 1/1000, \$5.00; merthiolate 1/1000, \$9.30; metaphen 1/500, \$12.50; furmerane 1/3000, \$5.95; proflavine 1/1000, \$0.58; dett (dettol) 5 per cent, \$0.28 (pure dett is \$58.80 per dozen gal.); amphyl  $\frac{1}{2}$  per cent, \$0.01 $\frac{1}{4}$  (pure amphyl is \$2.50 per gallon).

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## CARBAMIDE-SULFONAMIDE MIXTURES IN WOUND THERAPY

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THE advantages of carbamide (urea) in the treatment of infected and contaminated wounds have been detailed elsewhere.<sup>1, 2</sup> The principle of carbamide action is that of a strong peptonizing and lytic agent for devitalized tissues. Carbamide action rids the wound of necrotic tissue by a process of chemical débridement. The action in markedly increasing the rate of healing of infected wounds is on the basis of ridding the wound of deterrents to normal healing rather than by direct bactericidal action. Bacteriostasis results from removing the substances producing bacterial growth and multiplication. Further, this is accomplished without great detriment to the normal physiologic processes of wound repair and without material irritation or damage to normal tissue cells. Excellent results, attested by numerous favorable reports,<sup>3, 4, 5</sup> have followed our revival<sup>1</sup> of carbamide therapy which was first used by Symmers and Kirk.<sup>6</sup> Outstanding as have been the results in the limited field of infected wound therapy, much greater has become the applicability of carbamide in all phases of wound therapy since its combination in topical application with the sulfonamide drugs.<sup>7</sup>

Much has been written and considerable experience has been accumulated on the topical application of the sulfonamides. The bacteriostatic effect of these drugs is the supposed result of a specific interference with the enzymatic utilization by the bacteria of some nutritive chemical factor. The highly selective action of sulfonamides on bacterial metabolism is evidenced by bacteriostasis in the presence of concentrations of these compounds as low as 1 mg. per cent. When implanted directly into wounds these substances, like carbamide, show little demonstrable injury to normal tissue cells or interference with the mechanism of phagocytosis and ultimate tissue repair. The efficacy in the topical use of these compounds in bacteriostasis has been shown to be directly proportional to (1) concentration of sulfonamide inhibitors, (2) solubility and diffusibility, i.e., local concentration of the drugs, and (3) degree of active cellular defense within the wound.

### ENHANCEMENT OF SULFONAMIDE ACTION BY CARBAMIDE

Carbamide acts in a number of ways to enhance the action of the sulfonamides. In a preliminary report<sup>7</sup> presenting the results of wound

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therapy with carbamide-sulfonamide mixtures, the removal by the carbamide of gross sulfonamide inhibitors, or the source of such inhibitors, in the form of necrotic tissue, pus, and tissue exudates was stressed. The importance of this chemical débridement must not be minimized either for its direct action or its effect in removing the debris which gives rise to sulfonamide inhibitors. Clark and his co-workers<sup>8</sup> have recently demonstrated that the mere presence of carbamide antagonizes the sulfonamide-inhibitor action of at least one of the end products of protein catabolism. It is probably by antagonizing inhibitors that carbamide enhances the bacteriostatic action of the sulfonamides.

In vitro experiments have shown that ten times as much sulfanilamide is necessary to prevent the growth of a strain of *Escherichia coli* as when the sulfanilamide is used with 5 per cent carbamide. In this concentration the carbamide alone is not particularly bacteriostatic. Similar results were obtained with a strain of *Staphylococcus aureus* using sulfathiazole. Strakosch and associates<sup>9</sup> have reported the same type of results in vivo, using infected dermatoses for their study.

In our earlier study<sup>7</sup> the impression was gained that carbamide increased the solubility of the sulfonamide drugs. This desirable effect would not be an unreasonable result in view of the marked solvent action of aqueous carbamide solutions. Data on this point have been collected as follows.

#### SOLUBILITY DATA

Temperature, 37.5° C., per 100 Gm. of H<sub>2</sub>O:

<i>Carbamide</i>	<i>Sulfanilamide</i>
0	1.7 Gm.
20 Gm.	3.5 Gm.
40 Gm.	5.5 Gm.
60 Gm.	8.0 Gm.
100 Gm.	13.5 Gm.
<i>Carbamide</i>	<i>Sulfathiazole</i>
0	0.1 Gm.
10 Gm.	0.4 Gm.
30 Gm.	0.5 Gm.
60 Gm.	1.0 Gm.
80 Gm.	1.5 Gm.
100 Gm.	2.0 Gm.

Solubility in a carbamide solution (108 Gm. carbamide in 100 Gm. H<sub>2</sub>O) saturated at 20° C.:

20° C. at room temperature	{ Sulfanilamide	8.5 Gm.	
	{ Sulfathiazole	1.0 Gm.	
37.5° C. at body temperature	{ Sulfanilamide	15.0 Gm.	} per 100 Gm. H <sub>2</sub> O
	{ Sulfathiazole	2.4 Gm.	

Solubility in a carbamide solution (155 Gm. carbamide in 100 Gm. H<sub>2</sub>O) saturated at 37.5° C.:

37.5° C. body temperature	{ Sulfanilamide	27.5 Gm.	} per 100 Gm. H <sub>2</sub> O
	{ Sulfathiazole	4.0 Gm.	

The tremendous increase in the solution of the relatively insoluble sulfa drugs is obvious and the increased concentrations are not obtained by increasing the pH to a high point as in the case with the sodium salts of these compounds. We are of the opinion that this action of carbamide in securing more rapid solution of the sulfa drug used is one of the most important as far as topical application is concerned. This prevents the usual caking of the relatively insoluble sulfa drugs with the attendant foreign-body reaction and interference with the reparative healing process.

The degree of active cellular defense within the wound is aided by carbamide in that this substance sequesters and removes necrotic tissue which is rich in bacterial contamination. It is also probable that the hypertonicity of the solution leads to diapedesis and an increase in the reaction within the wound tissues. Carbamide has been shown by Olson and co-workers<sup>10</sup> to increase the rate of formation of granulation tissue in experimental animals. That it may retard the rate of epithelization<sup>10</sup> in contaminated or infected wounds is of little consequence for epithelial repair is not desired at the time it is used. As soon as the wound is covered with clean granulation tissue treatment with this mixture will have been discontinued.

If carbamide had none of its other known advantages its value as a diluent for the sulfonamides would almost be sufficient reason for its addition to these drugs. The mixture is not only more effective than a sulfonamide alone but is much cheaper. This feature as well as the toxicity limitations in the use of the sulfonamides allows of much greater freedom in the use of the mixture.

#### PRACTICAL ASPECTS OF THERAPY WITH CARBAMIDE-SULFONAMIDE MIXTURES

Largely from the information gained from the above solubility studies the following mixtures of carbamide (urea) and sulfonamide drugs have been used:

1. Carbamide	86 per cent
Sulfanilamide	14 per cent
2. Carbamide	82 per cent
Pectin	5 per cent
Sulfanilamide	13 per cent
3. Carbamide	80 per cent
Sulfanilamide	13 per cent
Sulfathiazole	2 per cent
Pectin	5 per cent
4. Carbamide	97.6 per cent
Sulfathiazole	2.4 per cent
5. Carbamide	87 per cent
Sulfanilamide	13 per cent
Sulfathiazole	2 per cent
6. Carbamide	89 per cent
Sulfanilamide	10 per cent
Sulfathiazole	1 per cent

Mixtures 1, 3, and 5 have been most commonly employed.

No attempt was made to sterilize the crystal mixtures but this would be desirable in wide scale use. Sulfapyridine offered no particular ad-

vantages. Sulfadiazine was also used but it did not appear to have any virtues not possessed by the cheaper drugs. Addition of proportionate amounts of sterile water and warming readily converts the crystalline mixtures into a solution, one or both meeting any practical therapeutic indication.

#### CLINICAL APPLICATION OF CARBAMIDE-SULFONAMIDE MIXTURES

*Use in First Aid.*—Carbamide-sulfonamide mixtures (C.S.M.) have been most satisfactorily employed as a first-aid application to contaminated traumatic wounds of all descriptions. The powder is generously sprinkled in all recesses of the wound and the wound covered with sterile gauze secured with an elastic pressure bandage such as a stockinet. The application of this mixture as a first-aid dressing may well prove to be its most important use. When sprinkled over a fresh wound the mixture (C.S.M.) tends to inhibit the growth of bacteria and chemically débride devitalized tissue. In civilian life a contaminated wound is not considered infected until six to twelve hours after the injury, the time depending upon the amount of damage to the tissues. Our experience indicates that with C.S.M. treatment formal surgery may be safely delayed long after twelve hours have elapsed. The rule that compound fractures in civil practice must be operated on within this period may be disregarded in many instances. In the handling of wounds resulting from military action this extended period during which a wound may be kept from becoming infected provides for delay in evacuation of wounded and their transportation to facilities allowing adequate treatment. Also, when large numbers of casualties are brought in at one time the emergency treatment may allow patients to be operated upon in the order of their urgency. It further permits the adequate treatment of shock during this initial period thereby rendering the patient the best possible risk for definitive surgical treatment.

*Use in Formal Surgery in Civil Practice.*—The primary closure of contaminated wounds, particularly those involving fractures, is a question about which there is some difference of opinion in civil practice. However, it is now the custom of many experienced surgeons.<sup>11</sup> Whether or not it is attempted must depend upon the nature of the wound, facilities, and circumstances as well as the skill of the surgeon. The early treatment of fresh wounds with C.S.M. is a most important factor in making primary closure possible if formal surgery is feasible within a reasonable length of time. Therefore, many contaminated (not infected) wounds may be closed by primary suture without drainage after a careful débridement. Primary healing has been obtained. Following the accepted preparation of the skin and area surrounding contaminated wounds (special care being taken not to introduce irritating and lytic skin antiseptic solutions or even irritating soap solutions into the actual wound) the toilet of the wound itself, before accurate débridement, is accomplished with copious irrigation within a solution of C.S.M.



This is followed by careful débridement (wound excision when possible) and the crystalline mixture of carbamide-sulfonamide is generously dusted into the wound and closure then done with interrupted silk sutures without drainage. Drains, we feel, may introduce further contamination but more particularly are undesirable because they introduce air into any wound producing a fluid level with the inevitable escape of a portion of the rapidly dissolved carbamide-sulfonamide mixture, thereby preventing complete and rapid application of the mixture to all surfaces and recesses of the wound. Soft tissues are sutured as little as practicable, except the skin as noted above. Fractures of the bones are reduced and, if necessary, primary internal fixation is done without fear of complication. Always when possible, regardless of structures involved, immobilization of the part by plaster or compression dressing is employed for greater comfort to the patient and maximum aid to the reparative process. Primary closure of wounds in civil practice may be carried out safely when they are under close observation and when facilities are available for the continued observation of the patient. Primary suture should never be done if thorough débridement and effective wound hygiene cannot be accomplished because of the extent of the injury or lack of time. If infection should develop after closure, the skin sutures may be removed and the wound treated as an open one without fear of any added complication. The results of Ilfeld<sup>12</sup> of this staff, who is reporting a consecutive series of forty-two major contaminated traumatic wounds involving soft tissues, skeletal structures, and joints treated with C.S.M. primarily, followed by careful surgical preparation and débridement with primary interrupted suture of the skin without drainage, are most encouraging. In this series there were less than 3 per cent of wound complications, all of which were minor, and in no instance responsible for further morbidity or complications.

Experience of army surgeons in combat zones has emphasized the necessity for some method of open treatment of wounds as attempts at closed treatment even after formal surgery have generally been unsatisfactory.

*Use in Open Wounds.*—Wounds in which tissue loss prevents primary closure are treated by the daily application of C.S.M. after suitable surgery including adequate débridement. This is immediately productive of clean, healthy, rapidly growing granulation tissue which permits early successful skin grafting with attendant reduction of disability from scar tissue contraction as well as improvement in the final cosmetic result.

There is a great difference in the ability to get primary healing in civil practice and in battle casualties. War wounds should be left open and in the treatment of these C.S.M. should yield excellent results. A modification of the Orr "closed" treatment has been employed in suitable instances with excellent results. We have modified the original

technique by packing the wound with C.S.M. and covering only the surface of the wound with vaseline gauze before application of closed plaster.

Should an infected wound result because of the impossibility of suitable surgery or any other cause, treatment with C.S.M. yields even better results than the very excellent ones obtained with carbamide (urea) alone.<sup>1, 2, 3</sup> The mixtures are particularly useful in the closed plaster method of treating burns. Stonham<sup>4</sup> has commented on the usefulness of urea alone in this condition.

#### SUMMARY

Carbamide through a process of chemical débridement has been shown to have many virtues in the treatment of contaminated and infected wounds.

By its combination in topical application with the sulfonamide drugs the applicability of carbamide in wound therapy has been greatly extended. Carbamide removes the source of all and directly antagonizes at least some sulfonamide inhibitors as well as markedly increasing the solubility of the sulfonamide drugs. These factors all contribute to enhancing the efficacy of the sulfonamides.

Wound therapy with carbamide-sulfonamide mixtures is simple and inexpensive; results are excellent. Application as a first-aid measure is most useful in prolonging the period during which it is safe to do definitive surgery.

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# THE PATHOGENICITY OF BACTEROIDES MELANINOGENICUS AND ITS IMPORTANCE IN SURGICAL INFECTIONS

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**B**ACTEROIDES *melanogenicus* is a small, Gram-negative, anaerobic nonsporulating, black pigment-producing rod which was first isolated in 1921, by Oliver and Wherry<sup>1</sup> from the "throat, tonsils, infected surgical wounds of the abdomen, from urine collected as aseptically as possible, from a suspected focal infection of the kidney and from the feces of a case of chronic dysentery superimposed on an original amoebic infection." Although it was subsequently recovered by Burdon,<sup>2</sup> Varney,<sup>3</sup> Schwarz and Diekmann,<sup>4</sup> Cohen,<sup>5, 6</sup> Liebetrueth,<sup>7</sup> and Altemeier<sup>8</sup> from other pathologic processes including pyorrhea alveolaris, pulmonary abscesses, ruptured appendices, peritonitis, the uterus and blood stream in puerperal fever, etc., nevertheless, its role as a pathogen of special interest to surgeons has not been definitely established. According to Bergey and his associates *Manual of Determinative Bacteriology*,<sup>9</sup> it is: "Nonpathogenic for rabbits, guinea pigs and white mice. . . . Inhabits healthy mucous membranes of mammals but may take part in various pathological processes (Burdon)." Likewise, Shevky, Kohl, and Marshall<sup>10</sup> and Liebetrueth<sup>7</sup> who continued this work could find no evidence of its invasive capacity. The former remarked, "All attempts to show that *Bact. melanogenicum* had any significance as a primary or secondary invader in mixed infections gave negative results, so far as clinical evidence or attempts at experimental animal infections could be correlated."

Examination of their protocols reveals that fourteen to eighteen day old cultures were employed by the latter authors for intracutaneous inoculations.<sup>7, 10</sup> Since Burdon<sup>11</sup> has called attention to the fact that old cultures of *Bact. melanogenicus* may lose their viability, it is not surprising that virulence and invasiveness may, at times, also be lost. Moreover, since we have established the existence of immunologically distinct strains of this organism on the basis of specific proteins,<sup>12</sup> the occurrence of virulent as well as nonvirulent types of *Bact. melanogenicus* seemed also a likelihood.

From the data of Oliver and Wherry<sup>1</sup> and Burdon<sup>2</sup> as well as from our own observations (Table I) it was tentatively inferred that *Bact. melanogenicus* is an "opportunistic" (in the sense of Theobald Smith) which is capable of producing disease only when given a favorable opportunity to enter the tissues or when the natural resistance to in-

TABLE I

## ISOLATION OF BACTEROIDES MELANINOGENICUS FROM VARIOUS SURGICAL INFECTIONS

SEX AND AGE	CLINICAL DIAGNOSIS OR AUTOPSY FINDINGS	SOURCE OF MATERIAL	RESULTS OF BACTERIOLOGIC CULTURE
<i>A. Infections of the Respiratory Tract</i>			
1. M, 67	Subacute inflammation of throat	Biopsy: tissue left pharyngeal wall	Aerobic: <i>E. coli</i> , <i>Str. viridans</i> , <i>Staph. aureus</i> , Gram-negative diplococci Anaerobic: <i>Bact. melan.</i> , <i>Fusobacteria</i> , diphtheroids, small Gram-negative cocci
2. F, 36	Pulmonary abscess; terminal bronchopneumonia	Biopsy: tissue from pulmonary abscess	Anaerobic: <i>Bact. melan.</i> , <i>Fusobacteria</i> , <i>Str. (hemol.) Staph. albus</i> (hemol.)
3. M, 42	Bronchiectasis (bilateral)	Sputum	Aerobic: <i>Str. viridans</i> , <i>K. freundleri</i> , <i>M. catarrhalis</i> , diphtheroids, <i>Staph. albus</i> Anaerobic: <i>Bact. melan.</i> , <i>Fusobacteria</i> , diphtheroids, Gram-negative cocci
4. F, 29	Lobectomy for bronchiectasis	Pleural fluid	Aerobic: <i>Staph. albus</i> , <i>E. coli</i> , <i>Str. (nonhemol.)</i> , <i>Str. viridans</i> Anaerobic: <i>Bact. melan.</i> , diphtheroids, <i>Fusobacteria</i> , gram-negative cocci and small bacilli, <i>Cl. welchii</i>
5. M, 36	Empyema; postpneumonic abscess	Pus from abscess	Anaerobic: <i>Bact. melan.</i> , <i>Fusobacteria</i> , <i>Str. diplococci</i>
6. M, 50	None made	Pleural fluid	Anaerobic: <i>Bact. melan.</i> , <i>Str. diphtheroids</i> , <i>Fusobacteria</i> , Gram-negative bacilli
<i>B. Infections of the Gastrointestinal Tract</i>			
7. F, 52	Appendicitis with gangrene; diffuse peritonitis; diabetes mellitus	Pus from cul-de-sac	Aerobic: <i>E. coli</i> , <i>Str. (nonhemol.)</i> , <i>Str. viridans</i> Anaerobic: <i>Bact. melan.</i> , <i>Cl. welchii</i>
8. F, 52	Perforation of cecum below appendix; ulceration and peritonitis	Pus from abdomen	Aerobic: <i>E. coli</i> , <i>Str. (nonhemol.)</i> Anaerobic: <i>Bact. melan.</i> , <i>Fusobacteria</i> , <i>Cl. welchii</i>
9. M, 40	Appendical abscess; generalized peritonitis	Pus from abscess	Aerobic: <i>E. coli</i> , <i>Str. diphtheroids</i> Anaerobic: <i>Bact. melan.</i> , Gram-positive bacilli (nonsporulating), <i>Str. nonhemol.</i>
10. M, 54	Ruptured diverticulum with abscess	Pus	Anaerobic: <i>Bact. melan.</i> , <i>E. coli</i> , <i>B. pyocyaneus</i>

\*Died.

TABLE I—CONT'D

SEX AND AGE	CLINICAL DIAGNOSIS OR AUTOPSY FINDINGS	SOURCE OF MATERIAL	RESULTS OF BACTERIOLOGIC CULTURE
11. M, 58	Perforated, gangrenous appendix; generalized peritonitis	Pus from abdominal cavity	Aerobic: <i>E. coli</i> Anaerobic: <i>Bact. melan.</i> , Str., diphtheroids, <i>Cl. welchii</i> , Gram-negative coccobacilli, <i>Fusobacteria</i>
12. F, 27	Acute gangrenous appendicitis with perforation	Abdominal fluid	Aerobic: Gram-negative coccobacilli, <i>Staph. albus</i> . Anaerobic: <i>Bact. melan.</i>
13. F, 78	Ruptured appendix; generalized peritonitis	Pus from abdomen	Aerobic: <i>E. coli</i> , Str. (nonhemol.), <i>B. proteus</i> . Anaerobic: <i>Bact. melan.</i>
14. F, 46	Appendectomy	Pus from abdomen	Aerobic: <i>E. coli</i> , Str. (nonhemol.), <i>B. proteus</i> Anaerobic: <i>Bact. melan.</i>
15. M, 31	Colostomy and ileostomy	Rectum	Aerobic: <i>Staph. albus</i> , Str. (hemol.), <i>Str. viridans</i> Anaerobic: <i>Bact. melan.</i> , <i>Cl. welchii</i> , Gram-negative bacilli
16. F, 20	Ischiorectal abscess (traumatic)	Rectal abscess	Anaerobic: <i>Bact. melan.</i> , diphtheroids
17. M, 60	Cellulitis of face; tooth infection	Tooth socket	Aerobic: <i>Str. viridans</i> , diphtheroids, <i>Staph. albus</i> Anaerobic: <i>Bact. melan.</i> , <i>Fusobacteria</i>
<i>C. Infections of the Genitourinary Tract</i>			
18. F, 30	Cesarean section	Vaginal smear	Aerobic: <i>Str. viridans</i> , <i>A. fecalis</i> , <i>Staph. aureus</i> Anaerobic: <i>Bact. melan.</i> , Str. (nonhemol.)
19. M, * 62	Diverticuli of bladder; terminal bronchopneumonia; prostatic hypertrophy	Urine	Aerobic: <i>E. coli</i> , Str. (nonhemol.), <i>B. pyocyaneus</i> , <i>B. proteus</i> Anaerobic: <i>Bact. melan.</i>
20. F, 29	Infected vaginal cyst	Pus from cyst	Anaerobic: <i>Bact. melan.</i> , diphtheroids, <i>Fusobacteria</i> , Str.
21. F, * 19	Perinephric abscess	Pus from abdomen	Anaerobic: <i>Bact. melan.</i> , <i>E. coli</i> (hemol.), <i>Staph. aureus</i> (hemol.), Str. (nonhemol.), <i>Cl. welchii</i> .
22. M, 2½	Pelvic abscess, probably result of ruptured appendix	Pus from colpotomy	Anaerobic: <i>Bact. melan.</i> , diphtheroids, <i>E. coli</i> , <i>Str. viridans</i>
<i>D. Miscellaneous Infections</i>			
23. F, 68	Abdominal abscess, iliac region	Pus from abscess	Aerobic: <i>B. proteus</i> , <i>E. coli</i> , Str. Anaerobic: <i>Bact. melan.</i> , Gram-negative sporebearing bacilli
24. M, 38	Infection of finger	Pus from finger	Anaerobic: <i>Bact. melan.</i> , diphtheroids, <i>Fusobacteria</i> , <i>Staph. aureus</i> and <i>albus</i> , <i>Str. viridans</i> , Str. (nonhemol.), Gram-negative diplococci

TABLE I—CONT'D

SEX AND AGE	CLINICAL DIAGNOSIS OR AUTOPSY FINDINGS	SOURCE OF MATERIAL	RESULTS OF BACTERIOLOGIC CULTURE
25. M, 58	Diabetes mellitus; prepatellar abscess of muscuiar and fascial tissue about knee and thigh; gangrene of scrotum	Leg stump and amputated leg	Aerobic: <i>Str. viridans</i> , <i>Str.</i> (nonhemol.), <i>Staph albus</i> , diphtheroids, <i>E coli</i> Anaerobic: <i>Bact. melan</i> , <i>Fusobacteria</i> , <i>Cl welchii</i>
<i>E. Cultures Taken at Autopsy</i>			
26. M, 62	Chronic interstitial nephritis; polyposis of stomach; diverticulum of sigmoid; intercurrent bronchopneumonia	Blood  Lung	Aerobic: <i>E. coli</i> , <i>Str</i> (nonhemol.) Anaerobic: <i>Bact. melan</i> , <i>Fusobacteria</i> Aerobic: <i>B. proteus</i> , <i>Str</i> Anaerobic: <i>Bact. melan</i> , <i>Fusobacteria</i>
27. M, 39	Hemangioma of mesentery; necrosis of ileum; peritonitis; septicemia; hydrothorax; hemorrhagic pneumonia; purulent bronchitis	Blood	Aerobic: <i>E coli</i> Anaerobic: <i>Bact. melan</i> , <i>Str.</i> , diphtheroids, <i>Cl welchii</i>
28. M, 59	Multiple emboli of small pulmonary arteries; pelvic peritonitis; postoperative perineal resection of sigmoid	Blood	Aerobic: <i>B. proteus</i> , <i>E coli</i> Anaerobic: <i>Bact melan</i> , diphtheroids, <i>Str</i> , <i>Cl welchii</i>
29. M, 52	Omphalectomy; acute pulmonary infarcts; extensive bronchopneumonia	Lung culture	Aerobic <i>Staph albus</i> , <i> aureus</i> (hemol.), <i>E coli</i> , <i>B. pyocyaneus</i> , <i>Sti viridans</i> Anaerobic: <i>Bact. melan</i> , <i>Cl welchii</i>
30. F, 19	Abscess in pouch of Douglas, bronchopneumonia; inflammation of psoas muscle	Pus from right lumbar region	Aerobic: <i>E. coli</i> , <i>Str viridans</i> , <i>Str.</i> (nonhemol.) Anaerobic: <i>Bact melan</i> , <i>Fusobacteria</i> , diphtheroids
31. F, 24	Lobectomy for bronchiectasis, serosanguineous pleural effusion; pericardial effusion; gangrene of left upper lobe, thrombosis of hilar veins, lobular pneumonia	Pericardium and lung	Aerobic: <i>Str. viridans</i> , <i>Sti</i> (nonhemol.), <i>E coli</i> , <i>S. albus</i> , <i>S aureus</i> Anaerobic: <i>Bact. melan</i> , diphtheroids, <i>Cl welchii</i> , Gram negative bacilli
32. M, 70	Pneumonia with pulmonary abscess	Pulmonary abscess	Aerobic: <i>Str. viridans</i> (nonhemol.), <i>Staph aureus</i> Anaerobic: <i>Bact melan</i> , <i>Fusobacteria</i> , diphtheroids
33. M, 77	Perforated appendicitis, localized pelvic peritonitis; terminal septicemia with gastric ulcerations and hemorrhage and acute pulmonary thrombosis; chronic cholecystitis and cholelithiasis	Peritoneum	Aerobic: <i>E coli</i> , <i>Str</i> Anaerobic: <i>Bact. melan</i> , <i>Fusobacteria</i>

TABLE I—CONT'D

SEX AND AGE	CLINICAL DIAGNOSIS OR AUTOPSY FINDINGS	SOURCE OF MATERIAL	RESULTS OF BACTERIOLOGIC CULTURE
34. M, 19	Appendicitis; peritonitis; pneumonia	Pus from abdominal cavity	Aerobic: <i>Staph. albus</i> , <i>E. coli</i> Anaerobic: <i>Bact. melan.</i> , diphtheroids
35. M, 63	Ileostomy (chronic ulcerative colitis); bowel obstruction	Peritoneal cavity	Aerobic: <i>B. proteus</i> , <i>E. coli</i> , Str. Anaerobic: <i>Bact. melan.</i> , <i>Cl. welchii</i> , Fusobacteria, diphtheroids
36. F, 55	Carcinoma of rectum; necrosis of pelvic floor; peritonitis	Peritoneal exudate	Aerobic: <i>B. proteus</i> Anaerobic: <i>Bact. melan.</i> , Fusobacteria, <i>E. coli</i> , Str.
37. F, 65	Gallstones; peritonitis	Peritoneal cavity	Aerobic: <i>E. coli</i> , <i>Staph. aureus</i> Anaerobic: <i>Bact. melan.</i> , <i>Staph. aureus</i> , Str. (hemol.), <i>E. coli</i>
38. F, 50	Secondary carcinomatosis following carcinoma of uterus	Pus from peritoneum	Aerobic: <i>E. coli</i> , <i>B. proteus</i> , Str., diphtheroids Anaerobic: <i>Bact. melan.</i> , <i>Cl. welchii</i> , Fusobacteria
39. M, 69	Perforation of cecum, generalized peritonitis; terminal bronchopneumonia	Peritoneum	Aerobic: Str. (hemol.), <i>E. coli</i> Anaerobic: <i>Bact. melan.</i> , <i>Cl. welchii</i> , Fusobacteria, diphtheroids
40. F, 32	Hodgkin's disease	Pus from abscess on spine	Aerobic: Gram-positive cocci, Str. Anaerobic: <i>Bact. melan.</i>
41. M, 39	Duodenal ulcer with perforations; generalized peritonitis; recent subtotal gastrectomy and gastrojejunostomy	Peritoneal fluid	Aerobic: Str. (hemol., non-hemol. and viridans), <i>E. coli</i> , <i>B. pyocyaneus</i> , <i>Staph. albus</i> , <i>Staph. aureus</i> Anaerobic: <i>Bact. melan.</i> , <i>Cl. welchii</i>
42. M, 27	Chronic nephritis; acute enteritis; arteriosclerosis of coronary arteries, aorta, spleen, and adrenals	Fluid in bowel	Aerobic: <i>Str. viridans</i> , <i>E. coli</i> , <i>Staph. aureus</i> Anaerobic: <i>Bact. melan.</i> , diphtheroids, <i>Cl. welchii</i> , Gram-negative cocci
43. F, 53	Wound infection with extension into subcutaneous tissues of abdomen and thorax; acute peritonitis and adynamic ileus; terminal bronchopneumonia	Sigmoid	Aerobic: <i>B. proteus</i> , <i>E. coli</i> , <i>Staph. albus</i> , Str. Anaerobic: <i>Bact. melan.</i> , <i>Cl. welchii</i> , Fusobacteria
44. F, 72	Diabetes, left leg amputated; stump infected; bronchopneumonia of left base; edema of lungs	Pus from leg	Aerobic: <i>B. proteus</i> , Str. (hemol.) Anaerobic: <i>Bact. melan.</i> , diphtheroids
45. M, 45	Perforation of duodenal ulcer; acute peritonitis; bronchopneumonia	Wound culture	Aerobic: <i>Str. viridans</i> , <i>Staph. albus</i> , <i>Staph. aureus</i> , <i>E. coli</i> Anaerobic: <i>Bact. melan.</i> , Fusobacteria, diphtheroids

fection is abnormally low.<sup>13</sup> We therefore undertook a reinvestigation of its pathogenicity and its role in surgical infections.

#### EXPERIMENTAL

*Use of Freshly Isolated Strains.*—Strains of *Bact. melaninogenicus* were isolated from the washed sputums of patients suffering from pulmonary abscess or bronchiectasis. The material was heavily scraped over the surface of several plates of hormone agar enriched with rabbit blood and incubated for four or five days at 37° C. in a Varney anaerobic phosphorus jar.<sup>14</sup> Tubes of Rosenow's glucose brain broth were also used, from which plates were streaked. Colonies were picked under a Zeissler stereoscopic binocular microscope and transplanted to fresh plates of blood agar. In preliminary experiments twenty-five white mice were injected intra-abdominally with three-day old transplants suspended in saline solution or in 5 per cent mucin, prepared according to the technique of Rake.<sup>15</sup> None of the animals died. The bacteria evidently succumbed to the defenses of the peritoneum. We therefore directed our attention to the possibility that this organism may produce only *local* tissue injury or that it needed special protection in order to multiply in the animal's tissues. Mice were inoculated subcutaneously in the groin with 0.05 to 0.1 c.c. of broth cultures. Edema and inflammation which persisted for twenty-four hours or longer were observed at the sites of injection.<sup>12</sup> Control animals injected with heat killed cultures showed no demonstrable lesions.

Five white rabbits were injected intracutaneously on the anterior surface of the hind leg with 0.5 c.c. of a suspension of *Bact. melaninogenicus* made up in cysteine hydrochloride broth. Three of the animals were sacrificed for examination twenty-four hours later. The infected limbs were hot, greenish-black, indurated and swollen to about three times their normal size. Upon removing the skin, the exposed muscles were darker than normal and intensely edematous. An exudate, visible in the subcutaneous tissue near the site of injection, extended all the way up to the axillary region where about 25 c.c. of foul, turbid fluid was present. The muscles of the lower extremities and of the chest wall were likewise discolored, friable, and had a foul odor. The blood vessels were of a very dark hue. The liver, spleen, and kidneys were congested. Cultures of these viscera and of the heart's blood were sterile, but *Bact. melaninogenicus* was isolated in pure culture from the muscles and exudate near the site of injection.

In two other animals of this series, which were sacrificed at the end of forty-eight hours, a pouch of fluid had accumulated in one site and ruptured through a necrotic area in the skin, leaving the muscle exposed. The neighboring lymph nodes were hemorrhagic and a bloody exudate was visible in one of the injected paws. The draining lymph nodes, the heart's blood, and viscera were sterile, but the organism was isolated from the infected muscle and exudate. Three control animals,



inoculated with similar suspensions of heat-killed organisms, presented negative results. In none of the animals was there any evidence of leucocytosis during life.

*Effect of Previous Tissue Damage.*—In order to test the possible effect of previous tissue damage on the pathogenicity of *Bact. melaninogenicus*, the hair on the backs of rabbits was closely clipped and a standardized dose of staphylococcal toxin (0.02 c.c.) combined with one-fifth of a unit of antitoxin was injected into a series of spots where the culture was inoculated forty-eight hours later. Control injections were made with heat-killed organisms. Inflammation, exudation, and necrosis were observed only where living bacteria were employed.<sup>12</sup> It was concluded that *Bact. melaninogenicus* is capable of producing severe, local tissue injury, especially in areas which had been previously damaged by bacterial toxin.

*Effects of Mucin.*—Since we recovered *Bact. melaninogenicus* from the respiratory, gastrointestinal, and genitourinary tracts where mucus is usually present (Table I), it seemed desirable to test the possible effect of mucin on its pathogenicity and invasiveness. Previous studies with a variety of other bacteria, including *Neisseria meningitidis*,<sup>16, 17</sup> *Haemophilus pertussis*,<sup>18</sup> *Eberthella typhosus*,<sup>19</sup> *Diplococcus pneumoniae*,<sup>2</sup> *Neisseria gonorrhoeae*,<sup>21</sup> *H. influenzae*,<sup>22</sup> *Fusiformis*,<sup>23</sup> and *Vibrio cholerae*,<sup>24</sup> have shown that their virulence is markedly increased when suspended in mucin. It has been suggested that mucin supplies the germs with an artificial capsule and interferes with the phagocytic capacity of the leucocytes and the bactericidal action of the animals' serum.<sup>25-27</sup>

Four rabbits were injected intradermally in several spots on the clipped skin of the back with 0.2 c.c. of a suspension made from a strain of *Bact. melaninogenicus* which had been freshly isolated from a rabbit which died after injection with this organism. Comparable sites were inoculated with cultures made up in 5 per cent granular mucin,\* adjusted to pH 7.15, according to the technique of Rake.<sup>15</sup> Control areas received either cultures killed by boiling for twenty minutes or with mucin alone. The extent of erythema was noted daily and the edema measured by means of calipers. It was observed that with the use of mucin, there was a very marked increase in the amount of erythema and edema, particularly in the latter. Thus, at the end of forty-eight hours when control areas measured 26 by 36 by 3 mm. the dimensions of those injected with living culture and mucin were two to three times as large. After seventy-two hours, when the controls (without mucin) were essentially negative, the experimental areas still showed marked edema and erythema. One of the rabbits died four days after injection. The entire abdominal wall was black and *Bact. melaninogenicus* was isolated from the underlying muscle wall as well as from the hearts' blood, liver, and spleen.

\*We employed granular mucin type 1701-W obtained from the Wilson Laboratories.

Smears made from areas inoculated with mucin and *Bact. melaninogenicus* showed in the Gram stain, a capsulelike substance surrounding the bacilli. This is essentially what has been observed by investigators who worked with other bacteria, as mentioned above.

*Presence of Fibrinolysin in Cultures of Bact. melaninogenicus.* In previous studies<sup>12</sup> we demonstrated the occurrence of fibrinolysin, a substance which dissolves human blood fibrinogen, in cultures of *Bact. melaninogenicus*. The presence of fibrinolysin is considered by many investigators as evidence of invasiveness or pathogenicity.

#### SUMMARY

Evidence has been presented that *Bact. melaninogenicus*, a small, Gram-negative, anaerobic, nonsporulating, black pigment-producing germ should be regarded as a pathogen which is of importance in surgical infections.

We have isolated it in combination with other aerobic and anaerobic bacteria from forty-five surgical cases representing various infected wounds, lesions of the pleura and peritoneum as well as of the gastrointestinal, respiratory, and genitourinary tracts. Others have cultivated it from the blood stream during puerperal infection. At autopsy we found it in the heart's blood, the peritoneum, and visceral organs.

Experimentally, we have shown that it possesses a fibrinolysin which permits it to dissolve human blood fibrinogen, thus interfering with one of the essential defense mechanisms of the inflammatory process, local fixation of microorganisms.<sup>28</sup> In cultures it produces a putrid, foul odor and together with the anaerobic *Str. putrificus* is responsible for the unpleasant odor of some types of pus.<sup>29</sup>

Strains of *Bact. melaninogenicus* were recovered from human lesions, which if inoculated within a few days after cultivation, were pathogenic for rabbits and mice. Intradermal injection produced in the former intense local inflammation, dermonecrosis, and, occasionally, death. Previous damage of the tissue by a bacterial toxin enhances the dermonecrotic properties of the germs. The use of mucin as a menstruum for suspending the bacteria, supplies them with a capsule, thus augmenting their pathogenicity and invasiveness.

*Bact. melaninogenicus* like *Bact. funduliformis*<sup>30, 31</sup> and certain other members of the genus *Bacteroides*, may therefore be regarded as an "opportunistic"<sup>13</sup> which must find conditions suitable for invasion and multiplication.

We are indebted to Drs. Harold Brunn, A. L. Brown, LeRoy Briggs, F. I. Harris, M. Groper, and others for the use of their clinical material.

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## EARLY POSTOPERATIVE WALKING

### I. THE INFLUENCE OF EXERCISE ON WOUND HEALING IN RATS

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THE controversy relative to the advantages and alleged dangers of early postoperative walking, inaugurated by the publication of Ries's<sup>1</sup> paper in 1899, continues. Since then an evolution in the regimen has resulted in emphasis being placed on getting the patient out of bed and walking within one to twenty-four hours after laparotomy or herniorrhaphy. This change is due to the gradual realization that bed rest, especially in the first few days, is a veritable breeding place for complications.

Although our personal experience in a small clinical series has been successful and the reports of other proponents of the principle of early ambulation have been highly favorable it is obvious that adequate quantitative and objective data should be collected which would definitely indicate the value of the procedure in its various disputed aspects. Fear of wound disruption has been the major deterrent to the acceptance of early postoperative walking. The present report deals with an attempt to determine experimentally the influence of exercise on the rate of healing of standardized laparotomy wounds produced in rats.

#### EXPERIMENTAL

*Method.*—Adult male rats were fed on a stock diet. They were kept in glass jars 17 cm. long and 9 cm. in diameter with a wire floor and wood shavings for cleanliness, and a wire face for feeding. They had just enough room to turn around.

Anesthesia was produced by the intraperitoneal injection of 4 mg. of nembutal per 100 Gm. of rat. Epilation was accomplished with a barium sulfide paste. The midline was marked, before draping, with malachite green and under aseptic technique a 5 cm. incision was made in the midline of the abdomen along the raphe extending down from the xiphoid. This was then sutured with Deknatel "moisture proof" C silk in two layers; one interrupted layer including peritoneum, muscle, and fascia with intervals of 5 mm. and taking bites of tissue of about 2 mm.; the other a running stitch of the skin. Knots were triple-throw.

Half of the rats had been trained for two days before operation on a motor-driven treadmill 24 cm. in diameter, revolving 9 r.p.m. After operation these were run for fifteen minutes each day including the day

of operation and the day of sacrifice. Occasionally the animals, though trained beforehand, hung on the periphery of the treadmill and would fall; it was felt that this simply increased their muscular effort. All, after a few experiences, learned to walk quietly. The controls were kept in their cages except for daily cleaning. The animals in both groups not healing per primam were discarded.

The tensile strength of the wound was determined by a slight modification of the method of Harvey.<sup>2</sup> A one-gallon glass jar was interposed in parallel between a mercury manometer, a compressed air tank and a delivery needle. This served to equalize the rise of pressure. The intraperitoneal needle, after introduction under anesthesia, was moved from side to side and felt with the finger to be free. In spite of this precaution it at times became engaged in retroperitoneal tissue and a generalized emphysema occurred when the air was turned on. To exclude this error the abdominal wall was incised after each reading of tensile strength and the position of the needle, left in situ, noted. When it was found engaged, the results were discarded. The end point was made sharp by sacrificing the animals under water and observing the escape of the first air bubble. The skin almost always gave way before the fascia.

Sections for microscopic study were taken after the animals were sacrificed. The entire abdominal wall was fixed in formaldehyde.

#### RESULTS

Our data are summarized in Table I and illustrated in Fig. 1.

TABLE I  
TENSILE STRENGTH OF STANDARD EXPERIMENTAL LAPAROTOMY INCISIONS

POST- OPERATIVE DAY*	NO.	CONTROL (MEAN RUPTURE POINT MM. HG)	NO.	EXERCISE (MEAN RUPTURE POINT MM. HG)	STANDARD ERROR OF DIFFERENCE
3	11	96.8	10	104.4	11.8
5	15	143.0	14	185.0	12.7
10	12	165.0	11	181.8	11.6

\*The day of operation throughout is counted the first post-operative day.

It is apparent that exercise does not adversely affect the wounds of the animals three days postoperatively since statistical analysis reveals the reliability of the difference to be only 0.6. However, on the fifth postoperative day the wounds of the exercised animals are stronger, the reliability of the difference between the groups being 3.3, which is statistically significant. By the tenth day postoperatively this difference disappears and the wounds in both controls and exercised animals are essentially the same (reliability of the difference is 1.4). The table and graph demonstrate further that the tensile strength of the incisions of the exercised animals reaches the maximum in five days while that of the controls requires ten days to attain the same resistance to disruption. This indicates that the wounds of the exercised animals healed more rapidly than did the wounds of the relatively immobilized rats.

## DISCUSSION

To our knowledge the only experimental data with reference to the influence of exercise on wound healing are those of Soloman,<sup>3</sup> Mason and Allen,<sup>4</sup> Kimbarovskiy,<sup>5</sup> and Reid.<sup>6</sup> Kimbarovskiy's paper is not accessible. The work of Soloman and of Mason and Allen deals with the special problem of tendon healing which is not germane to our subject. Reid's studies led him to believe that immobilization is a most important factor for primary wound healing. However, under the conditions of our experiments, exercise rather than immobilization seems to be the more valuable.

Our findings confirm the early views as to the stimulating effect of function on healing, which had their inception in the work of Julius Wolff.<sup>7</sup>

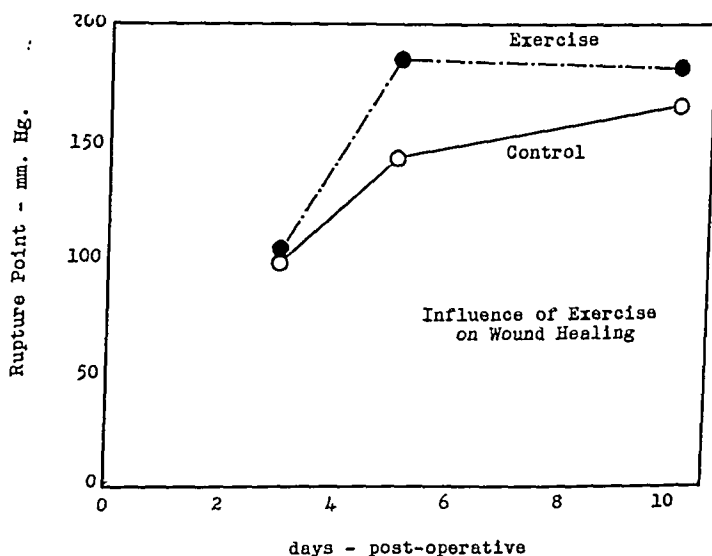


Fig. 1.—Illustrating the influence of exercise on the healing of standard abdominal incisions in rats.

An explanation of the increased tensile strength of the wounds caused by exercise at so early a period as the fifth day must be based on a shortened lag period or, conversely, a more rapid initiation of the period of fibroplasia. There is a latent period of about four days before the growth of fibroblasts becomes appreciable in terms of tensile strength. Howes<sup>8</sup> found new fibrils of collagen within two days in wounds sewn with silk and in three days with catgut. Immature collagen fibers are the only available agent for increasing strength as early as the fifth day. However, study of sections stained both with hematoxylin and eosin and with Masson's stain failed to show any constant variation in fibroblast activity or deposition of collagen between the exercised and unexercised groups.

Two particular items must be considered in the interpretation of our results. First, that the strength of the wound was determined by a relative and not an absolute method, and, second, that the rupture is a weakest-point rupture and so is not dependent on the strength of the sutures but essentially on actual healing of the tissues, and, to some extent, also on the holding power of the tissues for the sutures.

This study suggests that early postoperative walking with its attendant activity is not a factor in the etiology of postoperative wound disruption. In fact, it is even probable that postoperative walking will decrease the incidence of evisceration. However, such a conclusion with reference to man must await detailed analysis of clinical material.

#### SUMMARY

1. Standardized laparotomy wounds were produced in rats and at intervals of three, five, and ten days, the strength of the wounds was determined in animals which were kept at rest and in others which were exercised.

2. Exercise rather than immobilization was found to hasten the increase in tensile strength of the experimental abdominal incision.

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# A STUDY OF THE PHYSICAL FACTORS CONCERNED IN INFLAMMATION

## II. SOME FACTORS WHICH INFLUENCE THE SPREAD OF BACTERIA IN TISSUES\*

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### INTRODUCTION

IN A preceding communication, certain physical and physicochemical characteristics of inflammation have been defined and quantitated. It was demonstrated that an inflamed focus, whether clinical or reproduced in the laboratory, is the algebraic sum, so to speak, of opposing forces exerted on the two surfaces of the capillary wall. The initial mobilization of these forces is largely due to local chemical stimulation and partly to a reflex. However, the effort of the organism to deflect the activity of the irritant may become so intense and powerful that the irritant actually may be preserved due to the noxious, necrotizing effects of the inflammation itself.

It behooves the surgeon dealing with inflammation to consider the profound effects of elevation and rigid immobilization to reduce swelling, thereby augmenting capillary and venular circulation, and minimizing the spread of bacteria. The favorable results which have been obtained by so treating inflammations of various types attest to the sound physiology governing this method. Realizing that bacterial spread is a corollary of their growth cycle and, therefore, stimulates inflammation, the rates of spread of various bacteria and the factors governing the spread were investigated in the experimental animal.

### *Character of the Inflammatory Exudate*

*The Cellular Exudate.*—It is impossible to ascertain accurately the origin of the inflammatory cells. The polyvalent reticulum makes it difficult to define the limits of cytopoiesis. Although many authors support the hematogenous origin of cells in the inflammatory field (Baumgarten,<sup>8</sup> Ranvier,<sup>71</sup> and Schridde<sup>81</sup>), there is ample evidence that the local mesenchyme plays a large part in the production of inflammatory cells. Ranvier even spoke of "vasoformative" cells which could produce blood vessels and cells simultaneously—mesenchymal elements lying in the position of the pericytes and which are isolated reservoirs with embryonic potencies.

Although Wharton-Jones<sup>98</sup> distinguished between granular and non-granular white blood cells, Ehrlich<sup>28</sup> first described the use of stains

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to distinguish the cells. The granulocytes, the first leucocytes to arrive on the inflammatory field (Sherrington,<sup>83</sup> Muir,<sup>64</sup> Weiss,<sup>97</sup> Durham,<sup>26</sup> Borrel,<sup>12</sup> Beattie,<sup>9</sup> Bunting,<sup>14</sup> Ewing,<sup>30</sup> and Hardy<sup>47</sup>), have a varied heteroplastic origin: from the blood directly, local and emigrated lymphocytes (Feringa<sup>32</sup>), endothelium (Gerlach and Finkeldey<sup>41</sup>), and the local reticulum (Councilman<sup>13</sup>). The lymphocyte may be of local origin from the reticulum, the macrophages, or directly from the blood. The consensus of opinion is that the lymphocyte has the greatest potentialities of any cell in the inflammatory field, though the monocyte is often credited as being equipotential (Gay and Clark<sup>39</sup>). The monocytes are important, but microorganisms may multiply in their interiors and be disseminated further. Monocytes may originate only from fixed or free histiocytes (Wollenberg,<sup>99</sup> and Shiomi<sup>84</sup>) or from other monocytes (Bloom<sup>11</sup>), but there appears to be a morphologic interchange between the lymphocyte and the monocyte (Paremusoff,<sup>67</sup> and Frumkin<sup>38</sup>).

The histiocytes of normal unaffected regions of the body are stimulated by chemiotactic, hormonal, or autonomic influences so that the normal composition of the blood is altered with the resulting coursing of cells produced in the normal tissues to the area in distress (Sauerbruch,<sup>78</sup> Herzog,<sup>48</sup> Dominici,<sup>23</sup> and Ribbert<sup>76</sup>), but some investigators have doubted the value of this assistance. Maximow<sup>56</sup> has described three great cell types in the inflammatory field: (a) polymorphonuclear leucocytes; (b) polyblasts; and (c) fibroblasts. These categories include all the cell types.

The large phagocytosing macrophages (polyblasts) are (a) hematogenous (Michels and Globus<sup>61</sup>), from the lymphocytes and monocytes, and (b) histogenous, from local fixed or free histiocytes (Ziegler,<sup>100</sup> Foot,<sup>35</sup> Alfejew,<sup>4</sup> and Evans<sup>29</sup>). Adventitial cells (the vasoformative cells of Ranvier) are capable of forming polyblasts (Marchand,<sup>53</sup> and v. Recklinghausen<sup>72</sup>). The following names have been applied to the same cell: macrophage (Metschnikoff<sup>59</sup>), clasmatoocyte (Ranvier), vasoformative cell (Ranvier), rhagiocerin cell (Renaut<sup>74</sup>), histiocyte (Aschoff<sup>6</sup>), endothelial leucocyte (Mallory<sup>52</sup>), resting-wandering cell (Maximow), polyblast (Maximow), adventitial cell (Marchand), pyrrhol cell (Goldmann), wandering endothelial phagocyte, or anchored endothelial phagocyte (Cunningham, Doan, and Sabin).

In the inflammatory field are present many cells which seem to be not definite cell types but rather cells which bear the characters of two or more cells. Waldeyer<sup>93</sup> named them plasma cells because of their abundant cytoplasm, but later Unna<sup>91</sup> and v. Marschalko<sup>54</sup> described different cells which they also called plasma cells. According to Downey,<sup>24</sup> plasma cells are of histiocytic origin and are secretory in function.

Fibroblasts are present at the inflammatory focus about the time the monocytes and lymphocytes appear, and are seen to be laying down

fibers even during the active process in an attempt to wall off the septic area. Later they are present in great numbers, laying down heavy meshes of fibrous connective tissue, and comprising nearly the total number of cells in the field. They originate from fixed and free histiocytes (Babkina,<sup>7</sup> and Parker<sup>48</sup>), monocytes, lymphocytes, endothelium (Schaeffer<sup>49</sup>), and other fibroblasts. Maximow, who repeatedly emphasized that fibroblasts are end cells, incapable of further differentiation, was vigorous in his denial of the work of v. Möllendorff<sup>52</sup> who described amitosis of fibroblasts in inflammatory areas to form polyblasts, granulocytes, and nongranular cells. Identical observations were made by Marchand, Siegmund,<sup>55</sup> Weatherford,<sup>95</sup> and Benninghoff.<sup>10</sup> Ebeling<sup>27</sup> maintained that fibroblasts might multiply but never differentiate.

Tissue mast cells arise from nongranular cells (Weill,<sup>96</sup> and Staemmler<sup>97</sup>), but their function is debatable. They may be concerned in the removal of inflammatory debris (Ceelen,<sup>15</sup> and Addison<sup>3</sup>). Perhaps Danchakoff's view<sup>19</sup> that environment, not parentage, of a cell governs its potencies is the most accurate.

*The Serous Exudate.*—"Associated with these various changes we find increasing pouring of fluid from the tissues along the lymphatics, higher protein content of the discharged fluid and increased cell contents, both leucocytes and, it may be, red corpuseles. Such modified transudate is termed an exudate. In constitution it approaches more nearly to the blood plasma than does congestive edema fluid. It has, however, to be admitted that in different inflammations we find every transition from fluid of one type to the other . . ." (Adami,<sup>2</sup> and Mehu<sup>58</sup>).

### *Spread of Bacteria in Tissues*

Polymorphonuclears secrete a tryptic enzyme, acting in an alkaline medium, which neutralizes the blood serum antienzyme and yields supuration (softening and eroding) (Opie<sup>66</sup>). Staphylococci, which tend to evoke abscess formation, form a coagulase precipitating fibrin (v. Daranyi,<sup>20</sup> Chapman and associates,<sup>16</sup> Delezenne,<sup>21</sup> Fisher,<sup>33</sup> Gengou,<sup>40</sup> Gratin,<sup>43</sup> Gross,<sup>44</sup> Loeb,<sup>49</sup> Madison,<sup>51</sup> Much,<sup>63</sup> Vanbreuseghem,<sup>92</sup> and Walston<sup>94</sup>). On the other hand, fibrinolytic activity is possessed by hemolytic streptococci (Smith, Hankinson, and Mudge,<sup>86</sup> Tillett and Garner,<sup>89</sup> Pradhan,<sup>69</sup> and Dennis<sup>22</sup>) and pneumococci (Goodner,<sup>42</sup> and Rhoads and Goodner<sup>75</sup>).

Opposing the localizing effects of bacteria is the tendency of fibrinolysis and diffusion known as the spreading factor (Boyland and McClean,<sup>13</sup> Claude,<sup>17</sup> Angevine,<sup>5</sup> Favilli and McClean,<sup>31</sup> and Halban<sup>46</sup>). This spreading factor is present in many normal tissues (McClean,<sup>57</sup> and Duran-Reynals<sup>25</sup>). The tetanus toxin, for example, has an extraordinary ability to diffuse rapidly through tissues. It was formerly believed that the toxin traveled to the central nervous system via the endoneural and perineural lymphatics (Aschoff and Robertson,<sup>6</sup> Fletcher,<sup>34</sup> Friedemann and Elkeles,<sup>36</sup> Fröhlich and Meyer,<sup>37</sup> Gumprecht,<sup>45</sup> Loewi and Meyer,<sup>50</sup> Marie,<sup>55</sup> Meyer and Ransom,<sup>60</sup> and Teale

and Embleton<sup>88</sup>). Following Shdanow's<sup>82</sup> demonstration that no connection existed between the central nervous system and the lymphatics of the peripheral nerves, Abel<sup>1</sup> showed that the toxin was absorbed by the blood and then distributed to the central nervous system.

### *Statement of the Problem*

Since Menkin observed that the local swelling incident to inflammation mechanically isolates the infection and precludes central migration of bacteria, it was planned to determine the blocking effect to strychnine exerted by an inflammatory focus, since the physiologic effect of this drug is so striking.

It has been known that different bacteria possess different faculties of transmitting themselves in tissues (spreading factor); therefore, it was proposed to study the rate of transmission of various common bacteria. The diffusibility of tetanus toxin, which spreads extremely rapidly in tissues, suggested a satisfactory medium for studying the spreading factor of a pure toxin. Following this, the diffusibility of various dyes would be determined and then the bacterial spread defined by staining the injected bacterial suspensions with these dyes.

Because the spreading factor of an organism operates in a manner opposite to the local fixing power of the inflamed area, the degree of fibrinolytic and fibrinogenic power possessed by certain common staphylococci and streptococci warranted investigation.

## METHODS AND EXPERIMENTS

### *Spread of Toxins*

*Strychnine.*—To determine the diffusibility of strychnine sulfate from an inflamed area, 2 white rats, each weighing about 250 Gm., were etherized and the spine transected at the twelfth dorsal vertebra. Then, into a tarsal pad was injected 1.0 c.c. of 5 per cent strychnine sulfate. In a third rat, after transecting the spine, the left leg was immersed in boiling water for 1 minute. Twenty-five hours later, 1.0 c.c. strychnine sulfate was injected into the left tarsal pad. In a fourth rat, under ether anesthesia, the right tarsal area was circularly burned (using a hot nail), giving a ring-shaped burn. The following day 1.0 c.c. strychnine sulfate was injected into the right tarsal pad. In another etherized rat, the spine was transected at about the tenth dorsal vertebra, and a ring burn made in the skin of the right sural region the following day. Twenty-four hours later, 1.0 c.c. strychnine sulfate was injected into the right tarsal pad. The results of these experiments are given in detail in Table I.

*Tetanus.*—To determine the rate of absorption of tetanus toxin\* from the rat's tail, 31 rats were used. The tetanus toxin was supplied in evacuated vials from which fresh solutions were made. In this series of animals toxin was injected into the tip of the tail and the tail removed

\*The tetanus toxin was obtained through the courtesy of Mr. L. T. Clark, of Parke, Davis & Co., and Dr. E. G. Stewart of Eli Lilly and Company.

TABLE I

DIFFUSIBILITY OF FIVE PER CENT STRYCHNINE SULFATE SOLUTION THROUGH  
INFLAMED AREAS IN THE RAT

NO.	PROCEDURE	RESULT
a	1 c.c. into tarsal pad	Lethal convulsion 2 min. 20 sec.
b	1 c.c. into tarsal pad	Lethal convulsion 2 min. 20 sec.
c	1 c.c. into heat-inflamed area of leg	No convulsion; survival
d	Ring burn of leg; 1 c.c. into normal distal portion	No convulsion; survival
e	Ring burn of leg; 1 c.c. into normal distal portion	Convulsion 6 min.; death 9 min.

at its base with bone-cutting forceps under ether anesthesia at various intervals. No ligature is necessary after amputation since the bone cutter crushes the caudal vessels sufficiently for hemostasis. In some animals, the survival period after injection of the toxin directly into the heart cavity was compared with that after subcutaneous injection. The results of these experiments are similar to those obtained by Schimmelbusch.<sup>80</sup>

### *Spread of Bacteria*

Nissen<sup>65</sup> found that 5 minutes after injection of hundreds of thousands of *Bacillus anthracis* intravenously in rabbits, negative blood cultures were obtained; however, organisms were recovered from the liver, spleen, and bone marrow. Such is not the case, however, with *B. prodigiosus*, for when cultures of this organism are injected intraperitoneally, intravenously, or intratesticularly into rabbits, the rabbits are dead in 24 hours (Rosahn and Hu<sup>77</sup>). More recently, Reichel<sup>73</sup> found that intravenously injected bacteria were rapidly removed from the blood by antibodies and reticulo-endothelial tissues. Since virulence and invasiveness are different properties (Topley<sup>90</sup>), our experiments were performed with various organisms.

*Spread of Bacteria in Normal Tissues.*—In this series of experiments, 75 rabbits were used, the general procedure in each case being to make a subcutaneous injection of a bacterial suspension and then to take samples of subcutaneous tissue at definite distances from and including the injection point every four hours thereafter.

Bacterial counts were made in the following manner: The culture, usually on an agar slant, was suspended in sterile broth and diluted until the desired turbidity, as compared with a standard bacterial suspension, was reached; this gave the approximate count. Then, equal amounts of the suspension and blood from finger puncture obtained in a capillary pipette were blown out and mixed on a slide. A smear was then made which was stained with Wright's stain. Twenty-five fields were then counted under the oil immersion, the average erythrocyte count per field and average bacterial count per field being calculated. Then:

$$\frac{\text{Average number bacteria per field}}{\text{Average number erythrocytes per field}} = \frac{x}{5,000,000}$$

where  $x$  is the bacterial count per cubic millimeter. Assuming that the blood contained 5,000,000 erythrocytes per cubic millimeter,  $1000x$  gives the bacterial count per cubic centimeter.

In every case, 0.25 or 0.5 c.c. suspension was injected into the subcutaneous tissues over the tarsosural joint, and samples of subcutaneous tissue taken, usually every four hours, at 0, 3, 6, 9, and 12 cm. above the injection site, 0 referring to the sample taken directly from the injection site. Thus, five samples of subcutaneous tissue were taken from each animal, one rabbit being sacrificed every four hours. Although, in the first experiments, the leg into which the injection was to be made was depilated with barium sulfide prior to the injection, the depilation in latter experiments was deferred until the time of sampling since it was found that barium sulfide produces inflammation of sufficient intensity to cause serious consideration of its blocking effect on bacterial spread.

Sacrifice of the animal having been made by a blow over the occiput, ether or other blood contaminants being avoided because of their questionable effect on bacteria, the extremity of the rabbit was placed on several clean towels so that it was horizontal. An area considerably wider than that to be incised was thoroughly wetted by patting, not rubbing, water into the fur. Then the barium sulfide was sprinkled over the wet area and gently patted down into the hairs, any rubbing being studiously avoided in order to obviate any mechanical spreading effect. After 3 minutes, using clean cloths, the sulfide was wiped off gently from multiple areas, the wiping motion progressing from distal-to-injection site toward the injection site itself. In the same manner, the remainder of the sulfide was washed away with water, and then 70 per cent ethyl alcohol was flushed over the entire field followed by flushing with sterile 0.9 per cent sodium chloride solution.

All instruments having been sterilized, the skin 12 cm. above the injection site was incised and an area of subcutaneous tissue quickly cut away and placed in a sterile Petri dish for culture. The tissues from the 9, 6, 3, and 0 points were taken in the order named in order to avoid any possible contamination that might occur if tissues were taken in the reverse direction.

In the latter experiments, an attempt was made to compare the growth from actual tissue substance in the manner just described with growth from subcutaneous fluid. To obtain this fluid, five previously sterilized tuberculin syringes and No. 25 gauge hypodermic needles were used. Before an incision was made into a designated area for excision of tissues, 2 minims of sterile saline solution were injected subcutaneously into the area and quickly aspirated, rotating the syringe in order to prevent plugging of the needle opening. At best, only a trace of subcutaneous fluid is aspirable, even in distinctly edematous areas. The material so obtained was then quickly squirted into a sterile Petri dish for culture.

In nearly all of these experiments, a specimen from the spleen was cultured as an example of a reticulo-endothelial structure. Experiments (to be described later) showed that intravenous injections of large quantities of bacteria were entirely removed from the blood stream in 15 to 20 minutes. Therefore, in the rabbits injected subcutaneously, no blood cultures were obtained, but the spleen was cultured in order to determine if bacteria which rapidly spread subcutaneously were not also delivered into the blood and removed by the reticulo-endothelium. To obtain spleen specimens, the sacrificed animal was held supine and the skin of the entire abdomen rapidly reflected to each side with a sharp scalpel. Tincture of iodine was then flooded over the skinned abdomen and allowed to act for one to two minutes. Then using sterile instruments, a small incision through the abdominal muscles over the stomach was made, the spleen rapidly delivered into the wound by traction on the gastrosplenic omentum, and a piece cut off and placed in a sterile Petri dish. In order to avoid the bactericidal effect of iodine on any bacteria in the spleen, the instruments used to incise the iodized muscles of the abdomen were always discarded and fresh sterile instruments used to manipulate the spleen.

In the earlier experiments, it was thought advisable to determine the number of colonies grown on the Petri dishes in terms of unit tissue weight. For this purpose, previously weighed Petri dishes were used, the sample from the animal then being placed in a sterile dish and triturated with 5 c.c. sterile 0.9 per cent sodium chloride solution. The supernatant fluid, 1.0 c.c., was then pipetted into a sterile Petri dish for culture. The number of colonies grown  $\times 5$  was the total number of colonies per weight of tissues used. Then:

$$\frac{\text{Wt. of tissue (mg.)}}{1000} = \frac{\text{Number of colonies grown/weight of tissue}}{x}$$

where  $x$  is the number of colonies per gram of tissue.

The calculation of "number of colonies per gram of tissue" was not done in the latter experiments because (a) the initial tissue weights were too small to permit accurate weight differences in the Petri dishes, and (b) the procedure was considered as inviting contamination.

The samples of subcutaneous tissue, aspirated fluid, or spleen in the Petri dishes were cultured after flooding with agar previously melted at 100° C. and then brought to 35° C. before pouring over the specimen. Where blood agar was used, rabbit heart blood was obtained by aspiration through the anterior chest wall, the area being previously depilated, sterilized with full strength tincture of iodine, and cleared with Richardson's solution. Two large stock rabbits were kept for this purpose (ten pounds and twelve pounds), 40 c.c. of blood being taken at one time from a rabbit. The rabbits were used alternately in order to avoid too severe blood deprivation in a single animal and to allow the pectoral muscles to sterilize the previous needle tract before being used again.

The blood so obtained was always cultured before making the blood agar to be certain of its sterility, any question of contamination resulting in the discarding of the blood.

The specimens were cultured in an incubator at 38° C. and inspected from time to time; when the number of colonies reached the maximum they were counted, using a hand lens to see the more recent pin-point colonies, the number being recorded irrespective of size. The counting was facilitated by marking the Petri dishes with a glass marking pencil, subdividing each into several areas, each of which could be checked off. Usually, the final counts were made at the end of 48 hours after culture. Where the colonies were too numerous to be counted accurately, they were recorded as "innumerable."

In some preliminary experiments, specimens of liver as well as spleen were cultured, but because of bleeding incident to excision of either of these organs with constant contamination of the other by blood, only the spleen was used in succeeding experiments. In each experiment, a control animal injected with saline solution subcutaneously was sacrificed 24 hours after injection and tissue samples were cultured. In nearly every case there was found to be contamination with *Staph. albus* but not other organisms. The organisms used were: *Str. viridans*, 18 rabbits; *Str. hemolyticus*, 12 rabbits; pneumococcus type I, 6 rabbits; *B. prodigiosus*, 6 rabbits; *B. pyocyaneus*, 9 rabbits; *Staph. aureus* (stock; Connaught), 18 rabbits; *B. coli*, 6 rabbits.

*Diffusibility of Various Dyes:* Pohle<sup>20</sup> pointed out that many properties of dyes are important in determining their diffusibility through the capillary wall. Since we were interested in evaluating the spreading factor in certain bacteria using dyes it was necessary to determine the diffusibility of the dye chosen in our particular experimental animal.

In 5 individual rabbits, intramuscular injections into the thigh were made of 5 c.c. 20 per cent sodium thiosulfate solution, 5 c.c. 2 per cent Congo red, 5 c.c. 2 per cent trypan red, 5 c.c. 2 per cent indigo carmine, and 4 c.c. 2 per cent trypan blue, and samples of heart blood plasma and urine examined at various intervals for the injected substance. The urine was obtained by cystostomy and the blood by cardiac puncture. The sites of injection were also inspected to determine the degree of stain remaining at various intervals.

Since our main experimental animal for evaluating the spreading factor was to be the rat, the rates of diffusion of several dyes were determined in 12 rats. After shaving a small portion of the abdomen, 1 minim of the dye solution was injected subcutaneously on one side and intracutaneously on the other. The dyes used were India ink, 1 per cent Congo red, 1 per cent trypan blue, 1 per cent pontamine sky blue, 1 per cent methylene blue, and 1 per cent indigo carmine. The animals were sacrificed at 12 and 24 hours and after incision of the skin the areas were inspected for diffusion of the dyes.

To determine the difference in rate of spread of the dyes between subcutaneous and intramuscular injection, various dyes were injected intra-

muscularly in 24 mature piebald rats. Into six of them about 0.25 c.c. aqueous 0.8 per cent indigo carmine was injected into the crural muscles on the right. About 0.25 c.c. aqueous 1 per cent pontamine sky blue was injected on the left.

In a second group of 6 animals, 0.25 c.c. 2 per cent aqueous trypan blue was injected on the right and 0.25 c.c. 1 per cent on the left.

In a third group of six rats, about 0.25 c.c. aqueous 5 per cent methylene blue was injected on the right, and about 0.25 c.c. 1 per cent on the left.

In a fourth group of 6 rats, about 0.25 c.c. aqueous 2 per cent Congo red was injected into the crural muscles on the right and about 0.25 c.c. 1 per cent on the left.

One individual from each group was sacrificed by etherization and necropsied at 2, 4, 8, 14, 24, and 48 hours. The injected areas were incised and the density of the stain present was noted.

*Spreading Factor of Bacteria:* In this comparison nearly 700 rats were used. In general, the procedure consisted of mixing bacterial cultures with various dyes, injecting the colored culture subcutaneously in the rat, and determining the degree of spread from the original injection site at various time intervals thereafter by observing the diffusion of the color. Sterile broth, colored with dye, was used as a control for each type of bacteria. The dyes used were: trypan red, 1 per cent; trypan blue, 1 per cent; indigo carmine, 0.8 per cent; Congo red, 1 per cent; India ink; methylene blue, 1 per cent; and pontamine sky blue, 1 per cent.

The organisms used were: *Staph. albus*, *Staph. aureus*, *Str. hemolyticus*, *B. coli*, pneumococcus type I, *B. pyocyaneus*, *B. prodigiosus*, and *Cl. welchii*.

The organisms were each cultured in veal-infusion peptone broth. To 14 c.c. of broth culture 0.5 c.c. of dye was added using a tuberculin syringe fitted with a No. 25 gauge hypodermic needle. The bacterial count was made according to the method described. As controls, 0.5 c.c. of dye was added to 14 c.c. of sterile broth. Thus, for each experiment (one organism/type being used for one experiment), fourteen tubes were set up, seven containing broth culture mixed with dyes, and seven containing sterile broth mixed with dyes:

- |                               |                                      |
|-------------------------------|--------------------------------------|
| 1. Trypan red—culture         | 8. Trypan red—sterile broth          |
| 2. Trypan blue—culture        | 9. Trypan blue—sterile broth         |
| 3. Pontamine sky blue—culture | 10. Pontamine sky blue—sterile broth |
| 4. Indigo carmine—culture     | 11. Indigo carmine—sterile broth     |
| 5. India ink—culture          | 12. India ink—sterile broth          |
| 6. Congo red—culture          | 13. Congo red—sterile broth          |
| 7. Methylene blue—culture     | 14. Methylene blue—sterile broth     |

From each tube, 0.5 c.c. of mixture was aspirated with a tuberculin syringe fitted with a No. 25 gauge hypodermic needle and injected into five or seven rats in the subcutaneous tissue of the abdomen, the number of rats injected depending upon the times at which they were to be



sacrificed. Thus, if five rats were injected with each numbered mixture above, a total of 5 times 14 or 70 rats would be injected. At the time of sacrifice, one of each number above would be etherized, totaling fourteen etherizations. Thus, if it were intended to study at 2, 6, 12, 24, and 48 hours after the injection, 5 times 14 or 70 rats would be injected, and at the end of each designated time interval, 14 rats would be sacrificed.

At the time of sacrifice, the rat was laid supine, each "culture-dye" rat lying side by side with a control "sterile broth-dye" rat. The skin of the abdomen was slit open with a sharp scissors and reflected to either side. The diffusion and intensity of color of the subcutaneous tissue was examined and each infected rat compared with its control. Intensity of color was noted as 1 to 4, the range being from a trace to very heavy persistence of color. A trace cannot be strictly interpreted as indicating that the bacteria or its toxin had diffused into the rat's body, because a dye may leave a stained bacterium or the adsorbed toxin molecule and diffuse separately. In addition, the degree of diffusion from the original injection site was noted and designated as slightly diffused (s.d.), well diffused (w.d.), or all diffused (a.d.). A slight diffusion would mean a spreading of color just beyond the control diameter; well diffused indicates that nearly the entire abdominal subcutaneous tissue was stained; and all diffused would mean that not only the abdominal subcutaneous tissue was stained but the subcutaneous tissue of the thighs and back.

*Action of Bacterial Filtrates on Plasma Clots:* Although the work of other observers has demonstrated the presence of plasma coagulating substances in bacterial filtrates on citrated plasma, the following experiments were undertaken with a view of quantitating, if possible, the clotting phenomenon.

In one rabbit, freshly aspirated heart blood was citrated to 0.5 per cent with sodium citrate. The blood then was centrifuged and the plasma retained. The optimum recalcification time with 5 per cent calcium chloride solution was obtained, and 3 c.c. quantities of citrated plasma recalcified; 0.5 c.c. of a 225 million per cubic centimeter of saline suspension of *Staph. aureus* was added to the citrated plasma and the effects on the clot noted.

In another experiment, the staphylococcus suspension was filtered and the filtrate used in place of the whole suspension.

In a third experiment the staphylococcus filtrate was added to citrated plasma.

From an autopsy on a patient who had just expired from a streptococcal pneumonia, a fresh culture of gamma hemolytic streptococci was obtained from the pleural fluid on an agar slant, pure smears being obtained. The organisms were suspended in saline in a concentration of 100 million per cubic centimeter, and 0.5 c.c. of this suspension added to a 3 c.c. recalcified plasma clot. In another experiment 0.5 c.c. of a filtrate of the suspension was added to the recalcified plasma clot. In a

third experiment 0.5 c.c. of the filtrate was added to 3 c.c. of citrated plasma.

## RESULTS

*Spread of Toxins*

*Strychnine.*—In a group of 5 rats, it was found that if strychnine was injected into normal subcutaneous tissues, lethal convulsions would occur in 2 minutes 20 seconds. If the drug were injected into a heat-inflamed area, the animal survived. If injected below an inflamed area on the leg, the convulsions were either obviated entirely or delayed (Table I).

TABLE II

RATE OF ABSORPTION OF TETANUS TOXIN INJECTED INTO TIP OF RAT'S TAIL AND INTO HEART

NO.	AMT. INJECTED (MG.)	ROUTE OF INJECTION	INTERVAL BEFORE AMPUTATION (IN MIN.)	RESULT
1	.2	Heart	0	Dead in 2 days
2	.2	Heart	0	Dead in 4 days
3	.2	Heart	0	Dead in 2 days
4	.2	Heart	0	Dead in 2 days
5	.4	Heart	0	Dead in 2 days
6	.4	Heart	0	Dead in 2 days
7	.1	Tail	0	Dead in 8 days
8	.1	Tail	Immediate	Survived
9	.1	Tail	30	Dead in 7 days
10	.1	Tail	60	Dead in 5 days
11	.1	Tail	90	Dead in 2 days
12	.2	Tail	0	Dead in 4 days
13	.2	Tail	0	Dead in 2 days
14	.2	Tail	0	Dead in 2 days
15	.2	Tail	0	Dead in 3 days
16	.2	Tail	Immediate	Survived
17	.2	Tail	Immediate	Survived
18	.2	Tail	5	Survived
19	.2	Tail	10	Survived
20	.2	Tail	10	Dead in 5 days
21	.2	Tail	20	Dead in 3 days
22	.2	Tail	20	Survived
23	.2	Tail	30	Dead in 3 days
24	.4	Tail	0	Dead in 2 days
25	.4	Tail	Immediate	Survived
26	.4	Tail	5	Survived
27	.4	Tail	10	Dead in 3 days
28	.4	Tail	20	Dead in 5 days
29	.4	Tail	25	Dead in 3 days
30	.4	Tail	60	Dead in 2 days
31	.4	Tail	90	Dead in 2 days

*Tetanus.*—Tetanus toxin injected into the heart or tip of the tail in rats is equally lethal, death usually occurring in 2 days. If the tail is amputated within 10 to 20 minutes after the injection into the tip, the animal will survive. Usually the animal will die of tetanus if more than 5 to 10 minutes expires after injection before amputating the tail (Table II).

### Spread of Bacteria

*Spread of Bacteria in Normal Tissues.*—Following subcutaneous injection of bacterial suspensions in rabbits, organisms which spread rapidly (*S. viridans*, *S. aureus*, pneumococcus type I, and *B. coli*) were also found to an equivalent degree in the spleen. The rates of spread of these organisms are shown in Figs. 1, 2, 3, and 4. Some strains of *Staph. aureus*, *B. prodigiosus*, and *B. pyocyaneus* injected subcutaneously did not spread to any demonstrable degree as far as the culture technique is able to show. It was found that aspirated fluid in the infected field contained organisms when a great number could be demonstrated in culture of the whole tissue itself (Table III).

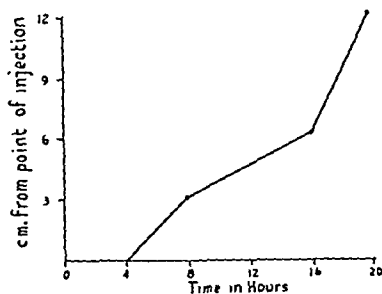


Fig. 1.

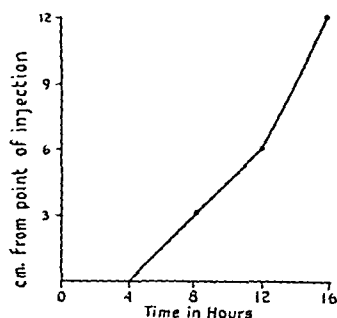


Fig. 2.

Fig. 1.—Rate of *Str. viridans* spread in subcutaneous tissue of the rabbit.

Fig. 2.—Rate of pneumococcus type I spread in subcutaneous tissue of the rabbit.

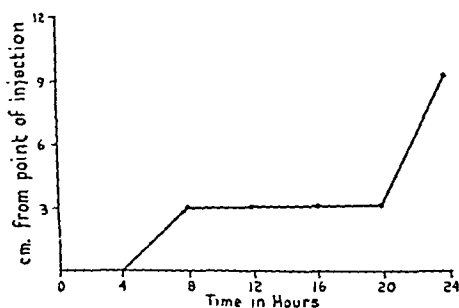


Fig. 3.

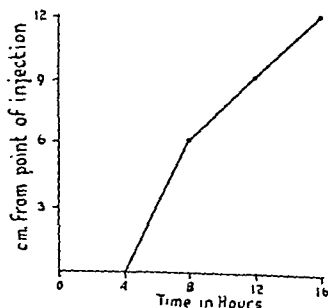


Fig. 4.

Fig. 3.—Rate of *Staph. aureus* spread in subcutaneous tissue of the rabbit.

Fig. 4.—Rate of *B. coli* spread in subcutaneous tissue of rabbit.

*Diffusibility of Various Dyes:* Congo red, given intramuscularly in rabbits, is found in slight concentrations in the blood and urine. Trypan red, however, injected similarly, is readily found in the blood, and indigo carmine is found in high concentrations in the urine. Trypan blue is rather indiffusible, remaining at the injection site (Table IV).

TABLE III

RATE OF BACTERIAL SPREAD IN RABBITS FOLLOWING SUBCUTANEOUS INJECTION; NUMBER OF COLONIES CULTURED AT VARIOUS DISTANCES FROM SITE OF INJECTION

NO.	NUMBER INJECTED	CM. FROM INJECTION	DISTANCES FROM SITE OF INJECTION						
			NO. OF COLONIES AT TIME INDICATED						
<i>A. Strep. viridans:</i>									
			1/2 HR.	3 HR.	4 HR.	24 HR.			
a	750,000,000	2	132 Gm.	18,333 Gm.	0	—			
b	1,880,000,000	2	1084	—	1084	—			
		4	—	—	—	0			
			4 HR.	8 HR.	12 HR.	16 HR.	20 HR.	24 HR.	
c	1,950,000,000	Spleen	0	0	0	0	0	0	
		Liver	0	0	0	0	0	0	
		0	5	Innum.	Innum.	Innum.	Innum.	Innum.	
		3, 6, 9, 12	0	0	0	0	0	0	
d	1,060,000,000	Spleen	0	0	0	0	Innum.	Innum.	
		Liver	0	0	0	0	Innum.	Innum.	
		0	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.	
		3	0	Innum.	0	4	Innum.	Innum.	
		6	0	0	0	Innum.	Innum.	203	
		9	0	0	0	0	Innum.	346	
		12	0	0	0	0	363	333	
<i>B. Strep. hemolyticus:</i>									
a.	775,000,000	Spleen	249	—	50	40	413	100	
		0	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.	
		3	18	121	100	25	53	45	
		6	49	350	61	47	30	50	
		9	246	1295	75	30	20	80	
		12	70	22	50	16	45	40	
			40 MIN.	80 MIN.	120 MIN.	160 MIN.	200 MIN.	4 HR.	
b	775,000,000	Spleen	27	27	85	46	25	68	
		0	150	107	290	429	58	21	
		3	57	52	57	156	17	147	
		6	24	30	31	125	24	0	
		9	50	36	16	7	51	0	
		12	20	40	9	50	96	240	
<i>C. Pneumococcus type I:</i>									
			4 HR.	8 HR.	12 HR.	16 HR.	20 HR.	24 HR.	
a	450,000,000	Liver	—	—	—	88	5	9	
		Spleen	—	—	—	297	13	264	
		0	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.	
		3	0	Innum.	Innum.	Innum.	Innum.	Innum.	
		6	0	0	Innum.	1134	Innum.	Innum.	
		9	0	0	0	244	12	2	
		12	0	0	0	39	0	894	
<i>D. B. prodigiosus:</i>									
a	500,000,000	Spleen	0	0	0	0	0	0	
		0 (tissue)	38	10	7	17	125	0	
		0 (fluid)	18	0	0	2	88	0	
		3 (tissue)	0	0	0	0	3	0	
		3 (fluid)	0	0	0	0	0	0	
		6 (tissue)	0	0	0	0	0	0	
		6 (fluid)	0	0	0	0	0	0	
		9 (tissue)	0	0	0	0	0	0	
		9 (fluid)	0	0	0	0	0	0	
		12 (tissue)	0	0	0	0	0	0	
		12 (fluid)	0	0	0	0	0	0	

Innum. = innumerable.

TABLE III—CONT'D

NO.	NUMBER INJECTED	CM. FROM INJECTION	NO. OF COLONIES AT TIME INDICATED					
<i>E. B. pyocyaneus:</i>								
			4 HR.	8 HR.	12 HR.	16 HR.	20 HR.	24 HR.
a	1,000,000,000	Spleen	0	0	0	0	0	0
		0 (tissue)	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		0 (fluid)	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		3 (tissue)	0	6	10	0	0	0
		3 (fluid)	0	0	Innum.	0	1	6
		6 (tissue)	0	0	0	0	0	8
		6 (fluid)	0	0	0	0	0	0
		9 (tissue)	0	0	0	0	0	0
		9 (fluid)	0	0	0	0	17	0
		12 (tissue)	0	0	1	0	0	0
		12 (fluid)	0	0	0	0	1	0
b	1,000,000,000	Spleen	0	0	—	2	—	0
		0 (tissue)	—	Innum.	—	Innum.	—	Innum.
		0 (fluid)	—	Innum.	—	Innum.	—	Innum.
		3 (tissue)	—	0	—	0	—	Innum.
		3 (fluid)	—	0	—	0	—	Innum.
		6 (tissue)	—	0	—	4	—	2
		6 (fluid)	—	0	—	0	—	0
		9 (tissue)	—	0	—	0	—	8
		9 (fluid)	—	0	—	0	—	0
		12 (tissue)	—	0	—	0	—	0
		12 (fluid)	—	0	—	0	—	0
<i>F. Staph. aureus:</i>								
a	1,650,000,000 (stock)	Spleen	0	0	0	0	725	0
		0	Innum.	Innum.	1	3	563	9
		3	4	28	0	0	26	0
		6	0	21	0	0	0	0
		9	0	0	0	0	0	0
		12	0	50	0	0	0	0
b	5,000,000,000 (Connaught)	Spleen	5	16	7	9	0	15
		0	Innum.	191	Innum.	47	4	156
		3	0	6	6	6	2	3
		6	0	0	0	0	0	4
		9	0	0	0	0	0	12
		12	0	0	0	0	0	1
c	2,665,000,000	Spleen	0	0	0	0	0	0
		0 (tissue)	2	Innum.	Innum.	57	13	5
		0 (fluid)	8	Innum.	Innum.	Innum.	0	1
		3 (tissue)	0	0	0	1	1	0
		3 (fluid)	0	0	3	0	0	0
		6 (tissue)	0	0	0	1	0	0
		6 (fluid)	0	27	0	0	0	0
		9 (tissue)	2	0	0	0	0	0
		9 (fluid)	0	0	0	0	0	0
		12 (tissue)	0	0	0	0	0	0
		12 (fluid)	0	0	0	0	0	0
<i>G. B. Coli:</i>								
a	1,105,000,000	Spleen	0	5	0	14	4	10
		0 (tissue)	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		0 (fluid)	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		3 (tissue)	0	29	Innum.	12	71	7
		3 (fluid)	0	4	6	0	6	3
		6 (tissue)	0	41	160	5	14	15
		6 (fluid)	0	3	0	15	8	11
		9 (tissue)	0	0	17	21	32	5
		9 (fluid)	0	0	16	3	4	5
		12 (tissue)	0	0	0	23	100	2
		12 (fluid)	0	0	0	1	13	14

TABLE IV

APPEARANCE IN BLOOD AND URINE OF VARIOUS SUBSTANCES INJECTED  
PARENTERALLY INTO THE RABBIT

NO.	SUBSTANCE	BLOOD	URINE	CONCENTRATION AT INJECTION SITE
a	Sodium thiosulfate	0	0	—
b	Congo red	Slight (4 hr.)	10 min.	—
c	Trypan red	Heavy	Trace	Heavy
d	Indigo carmine	Slight	Heavy	Slight
e	Trypan blue	0	—	—

In rats, pontamine sky blue, Congo red, indigo-carmin, and trypan blue diffuse best in the order named, after intracutaneous and subcutaneous injection. India ink was found to be indiffusible. Diffusion of methylene blue similarly injected cannot be evaluated because of the decoloration it undergoes in the tissues (Table V).

TABLE V

DIFFUSIBILITY OF PARENTERALLY INJECTED DYES IN RATS

DYE	12 HOURS		24 HOURS	
	SUBCUT.	INTRACUT.	SUBCUT.	INTRACUT.
Methylene blue	Not well dif- fused	Not well dif- fused	Not well dif- fused	Not well dif- fused
Pontamine sky blue	Both well dif- fused	Both well dif- fused	Both well dif- fused	Both well dif- fused
India ink	Poorly dif- fused	Poorly dif- fused	Poorly dif- fused	Poorly dif- fused
Indigo carmine	No trace	Localized	No trace	Localized
Trypan blue	Slight diffu- sion	Localized	Well diffused	Localized
Congo red	Well diffused	Well diffused	Well diffused	Well diffused

In a series of 24 rats, it was found that difference of concentration of a dye did not appear to influence its diffusion from an intramuscular injection site. Methylene blue, trypan blue, indigo carmine, and pontamine sky blue diffuse well from such areas (Table VI).

TABLE VI

DIFFUSIBILITY OF DYES INJECTED INTRAMUSCULARLY IN RATS IN DIFFERENT  
CONCENTRATIONS

TIME OF NECROPSY (IN HR.)	INDIGO CARMINE (.8%)	PONTAMINE SKY BLUE (1%)	TRYPAN BLUE		METHYLENE BLUE		CONGO RED	
			(2%)	(1%)	(5%)	(1%)	(2%)	(1%)
2	3	1	+	+	+	+	+	+
4	Trace	3	Dif.	Dif.	Dif.	Dif.	Dif.	Dif.
8	Faint trace	Trace	+	+	+	+	+	3
14	Absent	Diffusing	Dif.	Dif.	Dif.	Dif.	Dif.	Dif.
24	Absent	Absent	+	+	+	3	3	2
48	Trace	Absent	Dif.	Dif.	Dif.	1	3	2
			1	1	Trace	Trace	2 to 3	1
			Dif.	Dif.			Dif.	Dif.

Dif. = diffusing.

*Spreading Factor of Bacteria:* Bacteria which create severe inflammations (the rat is not subject to severe inflammations) form edematous areas at the subcutaneous injection sites wherein the dye is held. This is true for hemolytic streptococci, *Staph. aureus*, *B. coli*, and *B. pyocyaneus*. None of the organisms used grow well in the rat. In fact, the rat is quite resistant to any bacterial growth.

Indigo carmine, because of its great diffusibility, is of no value in determining spreading factor by this method. Methylene blue, because of its great diffusibility and greater tendency to become decolorized, should also not be used. Staphylococcus, in particular, exerts a strong decolorizing effect on methylene blue.

All the bacteria used caused the dye to diffuse better than the control broth-dye mixtures. Even the relatively indiffusible India ink diffuses better when mixed with bacterial suspensions. *S. aureus* and *S. albus* have definite spreading factors as tested by this method. *B. pyocyaneus*, *B. prodigiosus*, and pneumococcus type I show mild spreading factors (at least, in the rat). *Str. hemolyticus* appears to have a strong spreading factor. The Welch bacillus, however, has the most powerful spreading factor of all the organisms used; within 2 hours, the dye-Welch culture has diffused to all parts of the subcutaneous tissue of the rat (Table VII).

*Action of Bacterial Filtrates on Plasma Clots:* It was found that staphylococcus suspensions contain a fibrinolysin which can partly liquefy a plasma clot in some instances. On the other hand, certain staphylococcus filtrates contain a coagulase which clots citrated plasma (Table VIII, A).

Gamma hemolytic streptococcus suspensions liquefied plasma clots. A coagulase is, apparently, first formed by streptococci, and a fibrinolysin is formed later (Table VIII, B).

#### DISCUSSION

The blocking effect on the passage of strychnine past a burned area is largely a mechanical effect due to lymphatic block and coagulation of the intracellular matrix. The drug has a tendency, however, to leak into even the finest channels. This avidity for passage into the circulation is strikingly shown in the tetanus toxin experiments. This toxin is so rapidly absorbed from the tail tip that unless the tail is amputated at the base within 10 or 20 minutes after the injection of toxin into the tip of the tail, the animal will die of tetanus.

Although *Staph. albus* produces an exotoxin and leucocidin (destroying leucocytes), it does not usually have a powerful spreading factor. The staphylococcus may be dermonecrotic, hemolytic, or lethal. The relative production of coagulase or fibrinolysin may determine whether a patient will live with a boil or die of staphylococcemia. Streptococci appear to form a great deal of fibrinolysin, our experiments comparing well with the rapid spread of streptococci in living tissues.

TABLE VII

RATE OF SUBCUTANEOUS SPREAD OF BACTERIA (SPREADING FACTOR) STAINED BY  
VARIOUS DYES IN RATS

MIXTURE INJECTED	TIME OF EXAMINATION						
	2 HR.	4 HR.	6 HR.	12 HR.	24 HR.	36 HR.	48 HR.
<i>A. Staph. albus:</i>							
Trypan red—culture	4	—	w.d.	a.d.	a.d.	—	a.d.
Trypan red—broth	4	—	s.d.	a.d.	a.d.	—	a.d.
Trypan blue—culture	4	—	2	a.d.	a.d.	—	a.d.
	a.d.	—	w.d.	1	1	—	1
Trypan blue—broth	4	—	4	3	2	—	2
	s.d.	—	s.d.	s.d.	s.d.	—	s.d.
Pontamine sky blue—culture	3	—	2	a.d.	a.d.	—	a.d.
	a.d.	—	w.d.	1	1	—	1
Pontamine sky blue—broth	4	—	4	3	1	—	1
	s.d.	—	s.d.	s.d.	a.d.	—	a.d.
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	4	—	2	1	1	—	1
	s.d.	—	w.d.	a.d.	a.d.	—	a.d.
Congo red—broth	4	—	4	2	2	—	1
	a.d.	—	s.d.	w.d.	w.d.	—	a.d.
India ink—culture	4	—	4	4	4	—	4
	s.d.	—	s.d.	s.d.	s.d.	—	s.d.
India ink—broth	4	—	4	4	4	—	4
	s.d.	—	s.d.	s.d.	s.d.	—	s.d.
Methylene blue—culture	(Methylene blue oxidized to leuco base by staphylococcus culture after one-half hour contact)						
Methylene blue—broth	4	—	3	2	1	—	0
	w.d.	—	w.d.	w.d.	a.d.	—	0
<i>B. Staph. aureus:</i>							
Trypan red—culture	2	—	1	1	1	—	1
	w.d.	—	a.d.	a.d.	a.d.	—	a.d.
Trypan red—broth	4	—	1	1	1	—	1
	s.d.	—	w.d.	a.d.	a.d.	—	a.d.
Trypan blue—culture	2	—	1	1	1	—	1
	w.d.	—	w.d.	a.d.	a.d.	—	a.d.
Trypan red—broth	3	—	3	1	1	—	1
	s.d.	—	s.d.	a.d.	a.d.	—	a.d.
Pontamine sky blue—culture	2	—	1	1	1	—	0
	w.d.	—	w.d.	a.d.	a.d.	—	—
Pontamine sky blue—broth	4	—	3	2	1	—	0
	s.d.	—	s.d.	s.d.	w.d.	—	—
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	4	—	1	1	1	—	1
	s.d.	—	a.d.	a.d.	a.d.	—	a.d.
Congo red—broth	4	4	1	1	1	—	—
	s.d.	s.d.	w.d.	a.d.	a.d.	—	—
India ink—culture	4	3	3	2	2	—	—
	s.d.	s.d.	s.d.	s.d.	s.d.	—	—
India ink—broth	4	4	3	3	2	—	—
	s.d.	s.d.	s.d.	s.d.	s.d.	—	—
Methylene blue—culture	4	3	2	1	0	—	—
	s.d.	s.d.	s.d.	w.d.	—	—	—
Methylene blue—broth	4	4	3	1	0	—	—
	s.d.	s.d.	s.d.	w.d.	—	—	—



TABLE VII—CONT'D

MIXTURE INJECTED	TIME OF EXAMINATION						
	2 HR.	6 HR.	12 HR.	24 HR.	48 HR.	1 DAY	5 DAYS
<i>C. Str. hemolyticus:</i>							
Trypan blue—culture	4 w.d.	4 w.d.	3 a.d.	1 a.d.	1 a.d.	0 —	0 —
Trypan blue—broth	4 s.d.	4 s.d.	3 w.d.	1 s.d.	1 a.d.	0 —	0 —
Pontamine sky blue—culture	4 s.d.	2 s.d.	2 w.d.	1 a.d.	1 a.d.	— —	— —
Pontamine sky blue—broth	4 s.d.	2 s.d.	2 s.d.	1 a.d.	1 a.d.	1 a.d.	1 a.d.
Congo red—culture	4 s.d.	2 w.d.	2 w.d.	2 w.d.	1 a.d.	0 a.d.	0 —
Congo red—broth	4 s.d.	4 s.d.	2 w.d.	2 w.d.	1 a.d.	1 a.d.	0 —
India ink—culture	4 s.d.	4 s.d.	4 s.d.	3 s.d.	3 s.d.	2 s.d.	1 s.d.
India ink—broth	4 s.d.	4 s.d.	4 s.d.	3 s.d.	3 s.d.	2 s.d.	1 s.d.
Methylene blue—culture	4 s.d.	4 s.d.	4 w.d.	4 w.d.	2 w.d.	1 w.d.	1 w.d.
Methylene blue—broth	4 s.d.	4 s.d.	4 s.d.	1 s.d.	1 s.d.	1 w.d.	1 w.d.

*D. B. coli:*

	2 HR.	6 HR.	12 HR.	24 HR.	48 HR.
Trypan red—culture	4 s.d.	2 s.d.	2 a.d.	2 a.d.	2 —
Trypan red—broth	4 s.d.	2 s.d.	2 s.d.	2 w.d.	1 w.d.
Trypan blue—culture	4 s.d.	4 s.d.	2 s.d.	1 s.d.	0 —
Trypan blue—broth	4 s.d.	4 s.d.	2 s.d.	1 s.d.	— —
Pontamine sky blue—culture	4 s.d.	4 w.d.	3 w.d.	1 s.d.	1 w.d.
Pontamine sky blue—broth	4 s.d.	4 s.d.	3 w.d.	0 —	1 —
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	4 s.d.	4 s.d.	3 s.d.	2 s.d.	2 s.d.
Congo red—broth	4 s.d.	4 s.d.	3 s.d.	1 s.d.	1 s.d.
India ink—culture	4 s.d.	4 s.d.	3 s.d.	1 s.d.	1 s.d.
India ink—broth	4 s.d.	2 s.d.	2 s.d.	1 s.d.	1 s.d.
Methylene blue—culture	trace	trace	trace	trace	0
Methylene blue—broth	2	trace	trace	trace	0

*E. Pneumococcus type 1:*

Trypan red—culture	4 s.d.	3 s.d.	3 s.d.	2 w.d.	1 w.d.
Trypan red—broth	4 s.d.	3 s.d.	3 s.d.	2 s.d.	1 w.d.
Trypan blue—culture	4 s.d.	2 s.d.	2 s.d.	2 w.d.	1 w.d.
Trypan blue—broth	4 s.d.	2 s.d.	2 s.d.	2 s.d.	1 w.d.
Pontamine sky blue—culture	4 s.d.	—	3 s.d.	1 s.d.	1 s.d.

TABLE VII—CONT'D

MIXTURE INJECTED	TIME OF EXAMINATION				
	2 HR.	6 HR.	12 HR.	24 HR.	48 HR.
<i>E. Pneumococcus type 1:</i>					
Pontamine sky blue—broth	+	—	3	trace	trace
	s.d.	—	s.d.	—	—
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	+	3	3	2	1
	s.d.	s.d.	w.d.	w.d.	w.d.
Congo red—broth	+	3	3	2	1
	s.d.	s.d.	s.d.	s.d.	w.d.
India ink—culture	+	+	3	—	3
	s.d.	s.d.	s.d.	—	s.d.
India ink—broth	+	+	3	—	3
	s.d.	s.d.	s.d.	—	s.d.
Methylene blue—culture	+	1	trace	0	0
	s.d.	w.d.	—	—	—
Methylene blue—broth	+	3	3	trace	0
	s.d.	s.d.	s.d.	—	—
<i>F. B. pyocyaneus:</i>					
Trypan red—culture	+	+	1	0	0
	s.d.	s.d.	a.d.	a.d.	a.d.
Trypan red—broth	+	+	1	1	0
	s.d.	s.d.	w.d.	w.d.	a.d.
Trypan blue—culture	+	+	1	1	0
	s.d.	s.d.	w.d.	w.d.	a.d.
Trypan blue—broth	+	+	1	1*	0
	s.d.	s.d.	w.d.	w.d.	a.d.
Pontamine sky blue—culture	+	+	1	1	1
	s.d.	s.d.	a.d.	w.d.	a.d.
Pontamine sky blue—broth	+	+	1	1	0
	s.d.	s.d.	w.d.	w.d.	—
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	+	+	3	1	1
	s.d.	s.d.	s.d.	w.d.	w.d.
Congo red—broth	+	+	3	1	1
	s.d.	s.d.	s.d.	w.d.	w.d.
India ink—culture	+	+	3	2	2
	s.d.	s.d.	w.d.	w.d.	w.d.
India ink—broth	+	+	3	3	2
	s.d.	s.d.	s.d.	s.d.	s.d.
Methylene blue—culture	2	0	0	0	0
	s.d.	—	—	—	—
Methylene blue—broth	2	trace	0	0	0
	s.d.	—	—	—	—
<i>G. B. prodigiosus:</i>					
Trypan red—culture	+	3	3	2	2
	s.d.	w.d.	s.d.	s.d.	s.d.
Trypan red—broth	+	3	3	2	2
	s.d.	w.d.	w.d.	s.d.	s.d.
Trypan blue—culture	+	3	3	2	2
	s.d.	s.d.	s.d.	a.d.	a.d.
Trypan blue—broth	+	3	3	trace	trace
	s.d.	s.d.	w.d.	—	—
Pontamine sky blue—culture	+	+	trace	trace	0
	s.d.	s.d.	—	—	—
Pontamine sky blue—broth	+	+	3	trace	trace
	s.d.	s.d.	w.d.	—	—
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.

TABLE VII—CONT'D

MIXTURE INJECTED	TIME OF EXAMINATION				
	2 HR.	6 HR.	12 HR.	24 HR.	48 HR.
<i>G. B. prodigiosus</i> :					
Congo red—culture	4 s.d.	4 s.d.	3 w.d.	trace —	trace —
Congo red—broth	4 s.d.	4 s.d.	3 w.d.	trace —	trace —
India ink—culture	4 w.d.	4 w.d.	trace —	trace —	trace —
India ink—broth	4 s.d.	4 s.d.	3 s.d.	3 s.d.	3 s.d.
Methylene blue—culture	3 s.d.	trace —	trace —	trace —	0 —
Methylene blue—broth	4 s.d.	4 s.d.	0 —	0 —	0 —
<i>H. Cl. welchii</i> :					
Trypan red—culture	2 a.d.	1 a.d.	1 a.d.	1 a.d.	0 —
Trypan red—broth	4 s.d.	4 s.d.	3 w.d.	2 w.d.	0 —
Trypan blue—culture	2 a.d.	2 a.d.	1 a.d.	0 —	0 —
Trypan blue—broth	4 a.d.	4 w.d.	3 w.d.	3 w.d.	2 w.d.
Pontamine sky blue—culture	2 a.d.	2 w.d.	trace —	0 —	0 —
Pontamine sky blue—broth	4 s.d.	4 s.d.	3 s.d.	2 w.d.	0 —
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	1 a.d.	1 a.d.	1 a.d.	1 a.d.	0 —
Congo red—broth	4 s.d.	4 s.d.	3 s.d.	2 w.d.	trace —
India ink—culture	4 s.d.	4 s.d.	3 s.d.	3 s.d.	3 w.d.
India ink—broth	4 s.d.	4 s.d.	4 s.d.	3 s.d.	3 s.d.
Methylene blue—culture	0	trace	0	trace	trace
Methylene blue—broth	trace	trace	trace	trace	trace

1 = slight coloration.

4 = heavy coloration.

s.d. = slight diffusion of dye.

w.d. = well diffused; dye diffused nearly all over abdominal subcutaneous tissue.

a.d. = all diffused; dye diffused over subcutaneous tissue of entire body.

n.d. = no trace of dye visible at two hours.

## CONCLUSIONS

1. Tetanus toxin has a spreading factor so powerful that sufficient quantity for lethal issue may diffuse into the general circulation in 10 to 20 minutes after subcutaneous injection.

2. In the rabbit, *S. viridans*, *S. aureus*, pneumococcus type I, and *B. coli* spread rapidly, while *B. prodigiosus* and *B. pyocyaneus* and some strains of *S. aureus* spread slowly in the subcutaneous tissues.

3. Congo red, trypan red, indigo carmine, and trypan blue diffuse best in the order named in the rabbit. In rats, the order is maintained; however, pontamine sky blue is most diffusible and India ink least diffusible.

TABLE VIII

## EFFECT OF BACTERIAL FILTRATES ON RABBIT PLASMA CLOTS AND CITRATED PLASMA

NO.	MIXTURE	RESULT
<i>A. Staphylococcus filtrate:</i>		
a	Optimum recalcification time	3 min. 45 sec.
b	3 c.c. recalcified plasma	Remained clotted 2 days
c	3 c.c. recalcified plasma plus 0.5 c.c. saline solution	Remained clotted 2 days except for serum exudation
d	3 c.c. recalcified plasma plus 0.5 c.c. staphylococcus suspension	Partial dissolution of clot in 48 hr.
e	Optimum recalcification time	3 min. 55 sec.
f	3 c.c. recalcified plasma	Remained clotted 2 days
g	3 c.c. recalcified plasma plus 0.5 c.c. saline solution	Remained clotted
h	3 c.c. recalcified plasma plus 0.5 c.c. staphylococcus filtrate	Remained clotted
i	Optimum recalcification time	3 min. 45 sec.
j	3 c.c. recalcified plasma	Remained clotted 2 days
k	3 c.c. citrated plasma	Remained unclotted 2 days
l	3 c.c. citrated plasma plus 0.5 c.c. staphylococcus filtrate	Firm clot in 7 hr.
m	3 c.c. citrated plasma plus 0.5 c.c. saline solution	Remained unclotted 2 days
<i>B. Streptococcus filtrate:</i>		
a	Optimum recalcification time	4 min. 10 sec.
b	3 c.c. recalcified plasma	Remained clotted 2 days
c	3 c.c. recalcified plasma plus 0.5 c.c. saline solution	Remained clotted
d	3 c.c. recalcified plasma plus 0.5 c.c. streptococcus suspension	Dissolving of clot in 14 to 16 hr.
e	Optimum recalcification time	5 min. 33 sec.
f	3 c.c. recalcified plasma	Remained clotted 2 days
g	3 c.c. recalcified plasma plus 0.5 c.c. saline solution	Remained clotted 2 days
h	3 c.c. recalcified plasma plus 0.5 c.c. streptococcus filtrate	Dissolved clot in 7 to 8 hr.
i	Optimum recalcification time	4 min. 10 sec.
j	3 c.c. recalcified plasma	Remained clotted 2 days
k	3 c.c. citrated plasma	Remained unclotted 2 days
l	3 c.c. citrated plasma plus 0.5 c.c. saline solution	Remained unclotted 2 days
m	3 c.c. citrated plasma plus 0.5 c.c. streptococcus filtrate	Partial clot in 10 to 12 hours with complete dissolution of clot so formed in 48 hr.

4. In the rat, determined by the dye method, *S. aureus*, *S. albus*, *S. hemolyticus*, *B. pyocyaneus*, *B. prodigiosus*, and pneumococcus type I have mild spreading factors, the most powerful being *Cl. welchii*.

5. The staphylococcus and streptococcus both produce a fibrinolysin and a coagulase, as tested on plasma clots and citrated plasma.

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# AN ANALYSIS OF THE REACTION OF THE HUMAN GALL BLADDER AND SPHINCTER OF ODDI TO MAGNESIUM SULFATE

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SOME time ago, the senior author in collaboration with C. L. Birch<sup>1</sup> demonstrated that several hydragogue cathartics (especially  $\text{MgSO}_4$ ,  $\text{Na}_2\text{SO}_4$ , and  $\text{MgCl}_2$ ) caused marked reduction in the volume of the human gall bladder, as calculated from cholecystograms, and that this loss in volume could be correlated with the appearance of "B" bile in the aspirated contents of the duodenum. At that time no method had been employed for measuring with equal accuracy the decrease in resistance of the human sphincter. Recently, however, Bergh and Layne<sup>2</sup> have obtained manometer readings of the reaction of the sphincter to  $\text{MgSO}_4$  by utilizing the now common postoperative procedure of draining ducts of choledochostomized patients with T tubes. These detailed measurements make possible, for the first time, a more discriminating analysis of the relative reaction of the gall bladder and sphincter to substances introduced into the duodenum. Accordingly, it has seemed desirable to restudy the effect of  $\text{MgSO}_4$  upon the gall bladder in a sufficiently large number of individuals to make comparisons with the sphincter studies significant.

With this object in view eighteen medical students, responding to a call for volunteers, were subjected to the usual routine of oral cholecystography. In fourteen individuals the preliminary films showed sufficiently strong gall bladder shadows to be traced. After a Rehfuß tube had been passed, a roentgenogram was made, and then 30 c.c. of a saturated solution of  $\text{MgSO}_4$  were injected into the duodenum (ten students) or into the stomach (four students, subjects in whom the tube could not be passed beyond the pylorus in the time available). Thereupon roentgenograms were made at 2, 4, 8, 12, 16, 20, 25, 30, 35, 40, and 45 minutes after the injections. Subsequently, the gall bladder shadows were traced, the changing volumes computed in accordance with the method previously described,<sup>3</sup> and the individual curves of evacuation plotted (Fig. 1). Finally, the percentage loss in volume was calculated (Table I) and the mean values plotted (see heavy solid line, Fig. 2) and compared with the mean curves obtained in earlier studies of the reaction of the gall bladder to egg yolk (see heavy dash line, one egg yolk by duodenal tube; light dash line, five yolks by mouth).

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## OBSERVATIONS

A comparison of these mean curves of evacuation of the gall bladder, as plotted in Fig. 2, leaves no doubt but that  $MgSO_4$  induces emptying of the gall bladder. However, it is much less effective than egg yolk, since

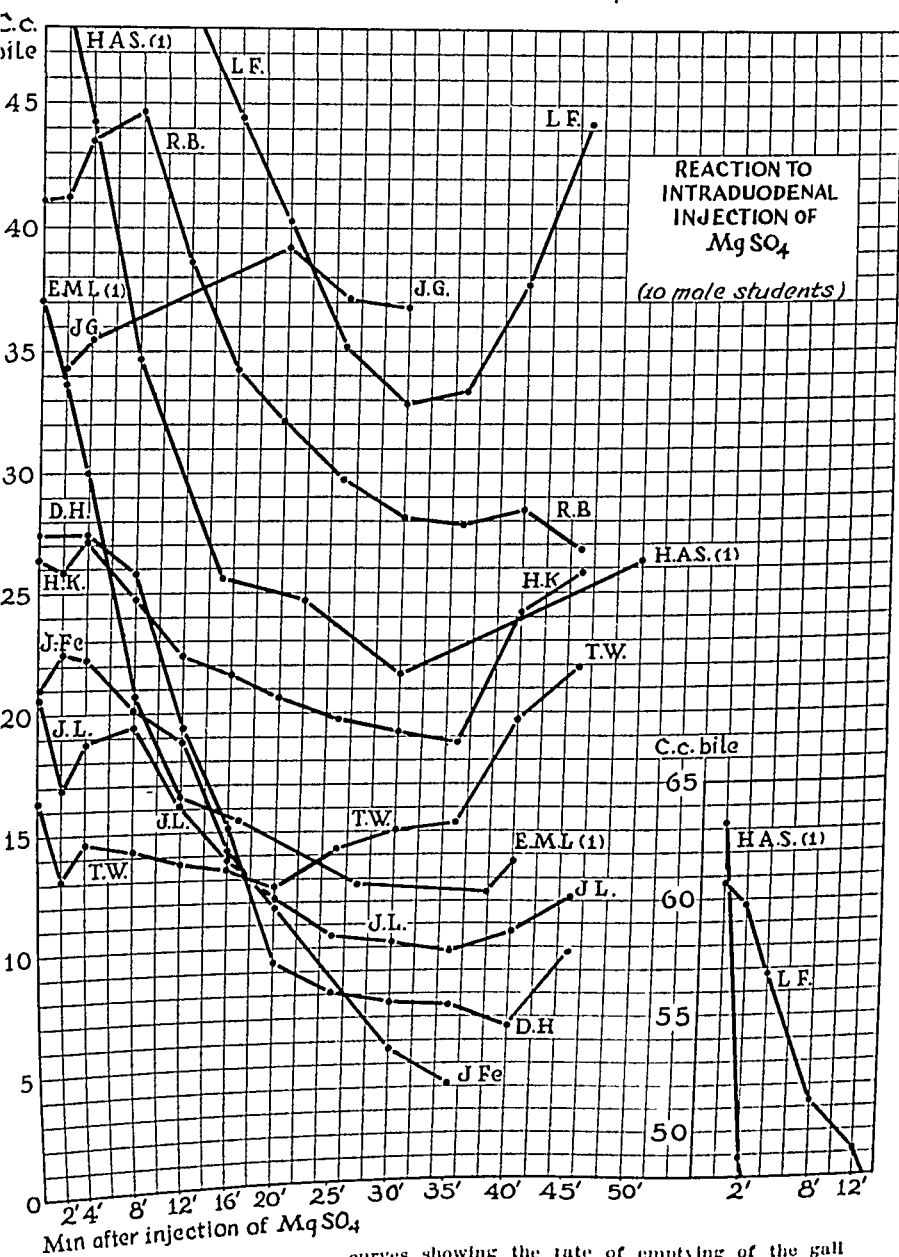


Fig. 1.—Curves showing the rate of emptying of the gall bladder in response to the injection of 30 c.c. of a saturated solution of  $MgSO_4$  intraduodenally (cf. Tables I and III). Ordinates, volume of gall bladder as calculated from cholecystograms (for method see Boyden). Abscissae, minutes after injection of salts into duodenum.

TABLE I  
REACTION OF HUMAN GALL BLADDER TO INTRADUODENAL INJECTION OF  $MgSO_4$

10 MALE STUDENTS	AGE	WT.	"B" BILE MIN.	VOLUME OF GALL BLADDER AT INTERVALS AFTER $MgSO_4$												PER CENT LOSS	C.C.	40 MIN.	PER CENT LOSS	C.C.	40 MIN.	PER CENT LOSS	C.C.	
				2 MIN.		8 MIN.		12 MIN.		20 MIN.		30 MIN.		40 MIN.										
				C.C.	PER CENT LOSS	C.C.	PER CENT LOSS	C.C.	PER CENT LOSS	C.C.	PER CENT LOSS	C.C.	PER CENT LOSS	C.C.	PER CENT LOSS									
R. B.	23	170	16	41.18(0)	00.00	(44.62)	38.67	6.10	32.13	21.98	28.20	31.52	(28.48)	31.52	31.52									31.52
J. Fe.	21	170	8	20.66(0)	2.13	20.22	18.89	8.57	11.81	42.84	5.76	72.12	4.13(35')	72.12	72.12									80.00
L. F.	21	165		59.63	14.36	51.07	40.15	17.58	40.29	32.44	32.91	44.81	(37.64)	44.81	44.81									44.81
J. G.	20	165		34.4	0.00	(35.37) (4')	-	0.00	(39.26)	0.00	(36.8)	0.00	-	0.00	0.00									0.00
D. H.	23	175	18	27.4(0)	5.37	25.93	19.29	29.60	9.40	65.69	7.65	72.08	6.59	72.08	72.08									75.95
H. K.	23	165	18	25.93	4.17	24.85	22.38	13.70	20.71	20.13	19.26	25.73	18.79(35')	25.73	25.73									27.54
J. L.	23	155	12	18.86	0.00	(19.43)	16.14	4.81	12.05	29.00	10.33	39.13	9.89(35')	39.13	39.13									41.72
E. M. L. (1)	24	152	8	33.66	38.50	20.7	16.38	51.34	14.32	56.63	12.70	62.77	12.42	62.77	62.77									63.10
H. A. S. (1)	21	155		63.18(0)	45.16	34.65	29.5	53.31	25.00	60.43	21.69	65.67	(23.95)	65.67	65.67									65.67
T. W.	23	150		13.08	0.00	(14.33)	13.72	0.00	12.30	5.96	(15.00)	5.96	(19.83)	5.96	5.96									53.62
Total	221	1622	80		109.69			185.01		335.10		419.79		419.79	419.79									436.27
Average	22	162	13.3		10.97			18.50		33.51		41.98		41.98	41.98									43.63
5 yolks by mouth—12 male students (Boyden, <sup>8</sup> Boyden and Grantlame <sup>9</sup> )					14.26			27.96		43.51		55.67		55.67	55.67									64.55
1 yolk by duod. tube—9 male students (Boyden and Berman <sup>5</sup> )					17.87			34.28		57.62		70.99		70.99	70.99									-

\*First noted in aspirated duodenal contents.

it causes discharge of only 42 per cent whereas egg yolk induces evacuation of 71 per cent of the contents of the biliary vesicle in the first 30 minutes after the fluid reaches the duodenum (Fig. 2 and Table I).

A similar statement regarding the action of  $MgSO_4$  upon the sphincter may be made by comparing the data of Bergh and Layne<sup>2</sup> with that of Bergh.<sup>4</sup> In these manometer studies of cholecystectomized patients with T tubes in the common duct it was observed that when  $MgSO_4$  was injected into the duodenum (Table IIB) the mean fall in resistance was only 3.1 cm. of water, whereas in fifteen patients receiving two egg yolks mixed with cream the fall averaged 7 cm. (Table II C).

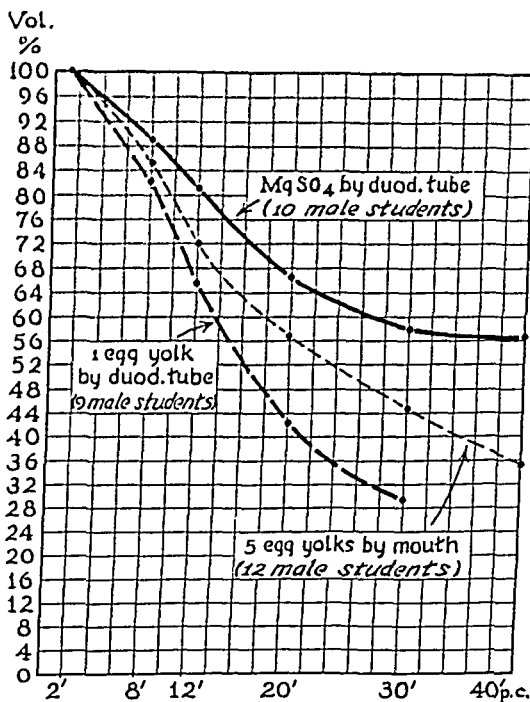


Fig. 2.—Mean curves comparing rate of emptying of the gall bladder in ten students receiving  $MgSO_4$  intraduodenally with rate in students of comparable age receiving egg yolk orally (cf. Boyden and Grantham)<sup>6</sup> and intraduodenally (cf. Boyden and Berman).<sup>3</sup> Ordinates, volume of gall bladder; abscissas, minutes after salts or egg yolk.

Secondly, these data indicate that although the effectiveness of  $MgSO_4$  is much less than that of egg yolk, it merely differs in degree, i.e. that it acts both upon the gall bladder and upon the sphincter for the same time and in the same way as egg yolk but with less force. Thus, under the stimulus of  $MgSO_4$ , emptying of the gall bladder first ceased 33.1 minutes after the drug had been administered (average for 9 students, Table IIIA) and with egg yolk, over 32 minutes afterward (average for 9 male students, Table IIIB).<sup>1, 5</sup>; with oral administration it took 32.5 minutes (average for 12 male students, Fig. 2).<sup>3, 6</sup> Similarly the maximum fall in sphincter resistance in the patients of Bergh and Layne occurred, respectively, at 21.4 and 21.7 minutes after  $MgSO_4$  had been

TABLE II  
EFFECT OF  $MgSO_4$  UPON SPHINCTER OF ODDI\*

PATIENT	FIRST RESPONSE (MIN.)	FALL BEGINS (MIN.)	MAXIMUM FALL (BELOW ORIGINAL LEVEL)		ORIG. LEVEL RECOVERED (MIN. AFTER DRUG)
			IN CM.	MIN. AFTER DRUG	
<i>A. Changes in resistance following oral administration of drug</i>					
1	0-up	6	3	47	54
2	0-up	4	8	26	60+
3	6-up	13	Remains above original level		
4	2-down	2	6	12	31
5	3-up	6	3	28	41
6	0-up	6	3	17	35
7	0-up	3	3	5	60
8	12-down	12	3	22	26
9	6-down	6	6	24	32
10	6-down	6	5	18	60+
11	4-down	4	1	6	7
12	4-down	4	5	30	49
Mean	12)43	12)72	11)46	11)235	11)455
	3.6	6	4.2	21.4	41.4
<i>B. Changes in resistance following injection into duodenum</i>					
1†	1-up	5	5	9	52
2	0-up	4	Returns to original level		
3	0-up	5	2	33	53
4	0-up	2	2	37	60+
5	0-up	6	2	14	24
6	4-up	8	1	10	12
7	0-up	10	6	18	34
8	0-up	4	4	26	45
9	0-up	2	Returns to original level		
10	0-up	3	Remains at high level		
11	0-up	2	1	12	24
12	0-up	4	5	36	48
Mean	12)5	12)55	9)28	9)195	9)352
	0.4	4.6	3.1	21.7	39.1
<i>C. 14 patients given 2 egg yolks and cream by mouth†</i>					
Mean	-	4	7	21	38

\*Analysis of data in article by Bergh and Layne<sup>3</sup> for comparison with gall bladder studies.

†These are not the same patients that are listed in A.

‡Bergh.\*

administered (average for 11 and 9 patients, Table IIA and B) and with egg yolk, 21 minutes afterward (average for 14 patients, Table IIC). Indeed, even the period of return to the original level of resistance was approximately the same—41.4 and 39.1 minutes for  $MgSO_4$  (Table IIA and B) and 38 minutes for egg yolk (Table IIC).

These parallel studies also permit a third major conclusion: namely, that while egg yolk and  $MgSO_4$  act for the same period and in the same way upon the gall bladder or upon the sphincter, and differ only in the degree of their effect, the end organs react differently to either stimulus. Thus, while emptying of the gall bladder continues until an average period of 31 to 33 minutes has elapsed after  $MgSO_4$  or egg-yolk has been administered, lowering of the sphincter resistance ceases after an average of 21 to 22 minutes; the figures for the actual duration of fall in volume

TABLE III  
ANALYSIS OF CONTRACTION CURVES OF GALL BLADDER

PATIENT	FIRST RESPONSE (MIN.) *	FIRST FALL BEGINS (MIN.)	MAIN FALL BEGINS (MIN.)	MAXIMUM FALL (BELOW ORIGINAL LEVEL)	
				MIN. AFTER IN- JECTION†	DURATION OF MAIN FALL
<i>A. Changes in volume following injection of 50 c.c. of MgSO<sub>4</sub> into duodenum in 10 male students</i>					
R. B.	0-up	8	8	35	27
J. Fe.	0-up	2	2	35	33
L. F.	0-down	0	0	30	30
J. G.	0-up	(20)	(20)	--	--
D. H.	0-up	4	4	40	36
H. K.	0-down for 2'	0	4	35	31
J. L.	0-down for 2'	0	8	35	27
E. M. L.	0-down	0	0	38	38
H. A. S.	0-down	0	0	30	30
T. W.	0-down for 2'	0	4	20	16
	0	9)14	9)30	9)298	9)268
Mean		1.5	3.33	33.1	29.8
<i>B. Changes in volume following injection of 1 egg yolk into duodenum in 9 male students†</i>					
W. F.	0-down	0	0	35+	35+
M. K. (1)	0-down for 2'	0	4	33+	29+
G. A. K.	0-down	0	0	25	25
E. D. P.	0-down	0	0	40+	40+
A. R.	0-up	2	2	30+	28+
M. M. S.	0-down	0	4	30+	26+
T. J. W.	0-down	0	0	32	32
A. D. W. (1)	0-down	0	0	27	27
A. D. W. (2)	0-down for 4'	0	9	38+	29+
	0	9)2	9)19	9)290	9)271
Mean		0.2	2.1	32.2+	30.1+

and of duration of resistance are approximately 30 and 17 (cf. column 6, Table IIIA and B, and the figure obtained by subtracting column 3 from 5 in Table IIB and C). Similarly, the initial response of the end organs to either agent is different. Thus, while the gall bladder in the majority of patients first reacts to one or the other stimulant by contraction (19 out of 24 individuals ingesting egg yolk, Table IIIC and D; 8 out of 9 taking egg yolk by tube, Table IIB; and 6 out of 10 individuals injected with MgSO<sub>4</sub>, Table IIIA), the sphincters first react in more than one-half of the patients by increased resistance (7 out of 14 patients ingesting egg yolk, Bergh,<sup>4</sup> 6 out of 12 taking MgSO<sub>4</sub> by mouth, Table IIA; and 12 out of 12 taking it by duodenal tube, Table IIB).

Finally, it may be noted that duodenal administration of MgSO<sub>4</sub> is no more effective in its action upon the sphincter than oral administration. The fall in resistance begins sooner with the duodenal injection ( $\pm 6$  minutes, Table IIB) than after ingestion of the drug (6 minutes, Table IIA) and ends sooner, but the total fall is slightly less (3.1 as against 4.2 cm.). No comparison is available for egg yolk.

In respect to the gall bladder reaction, only four individuals have been tested orally with MgSO<sub>4</sub>. Two of them averaged a discharge of



TABLE III—CONT'D

PATIENT	FIRST RESPONSE (MIN.)*	FIRST FALL BEGINS (MIN.)	MAIN FALL BEGINS (MIN.)	MAXIMUM FALL (BELOW ORIGINAL LEVEL)	
				MIN.	DURATION
				AFTER IN- JECTION†	OF MAIN FALL
<i>C. Changes in volume following oral administration of egg yolk to 12 male students§</i>					
L. J. B.	0-down	0	0	20	20
K. L.	0-down for 2'	0	4	25	21
I. D.	0-up	2	2	35	33
F. K. H.	0-down for 2'	0	4	20	16
N. A. C.	0-down for 2'	0	8	35	27
L. O. M.	0-down for 2'	0	4	45+	41+
J. S. L.	0-up	4	4	40+	36+
W. A. G.	0-down for 4'	0	12	45	33
R. C. C.	0-up	8	8	35	27
R. L. W.	0-down	0	0	20	20
R. J. B.	0-up	2	2	30	28
N. B. B.	0-down for 2'	0	4	40	36
	0	12)16	12)52	12)390	12)338
Mean		1.3	4.3	32.5	28.2
<i>D. Changes in volume following oral administration of egg yolk to 12 female students§</i>					
R. S.	0-down	0	0	20	20
F. E. D.	0 down for 4'	0	8	45+	37+
E. E.	0-down for 4'	0	8	30	22
C. L. B.	0-down for 2'	0	4	30	26
H. H. K.	0-down for 2'	0	4	25	21
K. L. L.	0-down for 2'	0	4	45+	41+
L. R. F.	0-down for 2'	0	4	25	21
A. H. H.	0-down	0	0	25	25
H. H. S.	0-up	8	8	45+	37+
S. M. O.	0-down	0	0	35	35
J. M. L.	0-down for 2'	0	4	30	26
C. H. S.	0-down	0	0	16	16
		12)8	12)44	12)371	12)327
Mean		0.7	3.7	31	27.25

\*Sometime between 0 and 2 minutes Pc. (Earlier studies, Boyden,<sup>3</sup> suggest the latent period is about 1 minute.)

†At this time falling begins.

‡From data of Boyden and Birch,<sup>1</sup> (Table I) as summarized by Boyden and Ber-man,<sup>5</sup> (Table III).

§After data in Boyden and Grantham,<sup>6</sup> Fig. 2.

45 per cent in 40 minutes but the other two showed little, if any, response to the drug. In the absence of a sufficient number of cases it can be stated merely that  $MgSO_4$  when administered orally may induce as marked emptying of the gall bladder as when given by duodenal tube. The studies on egg yolk are conclusive. When this food is given by duodenal tube it causes not only a more pronounced emptying (71 as against 55.7 per cent in the first 30 minutes, Table I; Fig. 2), but the initial response is quicker—the main phase of emptying beginning at an average of 2.1 minutes after duodenal administration (Table IIIB), as compared with 4.3 minutes after oral administration (Table IIIC).

Incidentally Table IIIC and D emphasizes the nature of the sex differences previously reported.<sup>3, 6, 7</sup> The data show that the time intervals are comparable, the main fall in volume for male students beginning at 4.3 minutes pc. and having a duration of 28.2 minutes, the cor-

responding figures for female students being, respectively, 3.7 minutes *pe.* and 27.25 minutes. Since, however, males of this age discharge approximately two-thirds of the contents of the gall bladder in the first 40 minutes after a meal of egg yolk and females nearly three-fourths (*cf.* Table III, Boyden and Puller),<sup>7</sup> it would seem either that the gall bladder contracts with greater force in the female or that the drop in sphincter resistance, in this sex, is greater. It would be desirable, therefore, to ascertain whether or not there are sex differences in the reaction of the sphincter to egg yolk.

#### DISCUSSION

The striking fact that  $MgSO_4$  acts for the same length of time as egg yolk and merely differs in the degree to which it affects the gall bladder or the sphincter strongly suggests that its mechanism is not local, as hitherto supposed, but hormonal and that it is absorbed by the intestinal epithelium and causes the formation of a cholecystokinin-like substance which stimulates the gall bladder to contract and the sphincter to relax. The fact that it does not cause as deep contraction or as great relaxation as egg yolk may be explained on the basis that magnesium is not absorbed as readily, or that it is not chemically so effective.\* In order to prove a hormonal mechanism it would be necessary to find an animal in which the biliary tract responds to magnesium sulfate† and to resort to such cross-circulation experiments as Ivy and Oldberg employed.<sup>10</sup> Nevertheless, it is believed that the circumstantial evidence presented above strongly favors the existence of such a mechanism.

The second striking fact—the differing reaction of the gall bladder and sphincter to a given stimulus ( $MgSO_4$  or egg yolk)—suggests the intrusion of a second factor. What is it that modifies the response of the sphincter, but not that of the gall bladder, to what is presumably an intestinal hormone? Reasoning from the data provided by animal and human experimentation, it may be assumed that the sphincter is under tonic contraction, except after meals, and therefore any force that releases it must overcome greater resistance than it would in the case of the gall bladder. Accordingly, if a given stimulus (e.g., a hormone in the blood) were applied at the same time to both the gall bladder and sphincter, its effect upon the sphincter might be expected to be delayed and, in the end, more quickly dissipated. In support of this it may be stated that sectioning of nerves to the biliary tract in cats leaves one with the inference that the sphincter is kept contracted by its own intrinsic nerve net rather than by extrinsic nerves, for when all nerves to the choledochoduodenal junction are severed the only effect is a marked retardation in the evacuation of the biliary tract after ingestion

\*According to Hirschfelder,<sup>8</sup> 20-30 Gm.  $MgSO_4 \cdot 7 H_2O$  by mouth does not significantly raise the blood magnesium, and about 40 per cent is excreted in the urine in 24 hours.

†Recently Kozoll and Necheles<sup>9</sup> have shown that magnesium and sodium sulfate have variable effects upon the sphincter of dogs and no effect on the gall bladder of that species. Similarly Boyden and Birch<sup>1</sup> were unable to induce contraction of the gall bladder in cats by injection of  $MgSO_4$  into the duodenum.

of egg yolk; i.e. the only extrinsic motor nerves that are eliminated by the experiment are the inhibitors of sphincter contraction (Johnson and Boyden<sup>11</sup>).

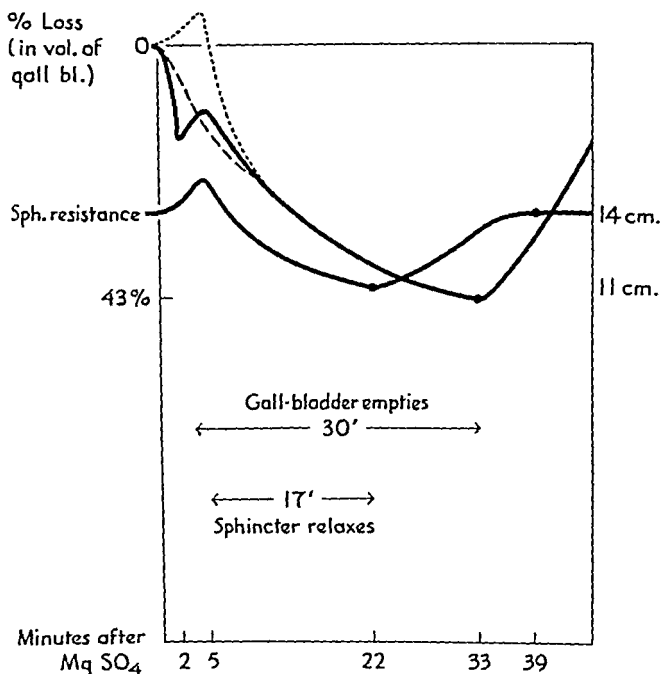


Fig. 3.  $MgSO_4$ , 10 gall bl. Fig. 1) it increase i. of events after duodenal administration of average decrease of 43 per cent in volume of ted line, 3 cases (R. B., D. H., and J. Fe., t reacted by relaxing, thereby appearing to line, 3 cases (H. A. S., L. F., and E. M. L.) in which the gall bladder reacted by contracting only; solid line, 3 cases (H. K., J. L., and T. W.) in which it first contracted (for 2 minutes), then relaxed (for an average of 3 minutes), then entered its main phase of contraction. Lower solid line, curve recording mean changes in resistance of sphincter in 12 patients (cf. Table IIB). In all 12, the sphincter reacted first by increasing its resistance (from an average manometer reading of 14. to 15.5 cm. of water), then its resistance fell gradually to 11 cm., then rose to 14. Note that the gall bladder empties for an average period of 30 minutes, while the sphincter relaxes for an average period of only 17 minutes.

Accepting these two hypotheses as starting points one may reconstruct the usual sequence of events as follows (Fig. 3). Within a minute or so after an effective substance enters the duodenum the gall bladder begins to contract under the stimulus of the circulating hormone. The sphincter, however, first reacts by increasing its resistance to the passage of bile, more so in the presence of  $MgSO_4$  than egg yolk. Quite likely this is the effect of local irritation upon a muscle already under sustained tonus. This rising resistance is maintained, on the average, for about  $4\frac{1}{2}$  minutes (Table IIB). If the period is shorter, probably the gall bladder continues to empty (dash line, Fig. 3); if longer, or more intense, the gall bladder probably relaxes (solid line, Fig. 3), usually for 2 or 3 minutes, the so-called "two-minute pause."<sup>3</sup> It is suggested that this sudden relaxation is the reaction of a local nerve net in the gall bladder wall to a suddenly increased load and that it is comparable

to what happens when bile backs up into the gall bladder during fasting; namely, the gall bladder adjusts itself to the increased pressure in the biliary tract.<sup>6</sup> Soon, however, the accumulating hormone prevails over the sphincter and the latter's resistance decreases for an average period of about 17 minutes (Fig. 3) until the level of the hormone drops below the threshold of the sphincter's nerve net; then resistance slowly increases for another 17 minutes until the original level of resistance is regained. Meanwhile, under the stimulus of the accumulating hormone, the gall bladder has resumed contraction and keeps it up for an average of 30 minutes until the sphincter resistance approaches its fasting level. This ends the first phase of emptying. A new spurt of food sets the mechanism going again.

It will be noted that the above account eliminates the necessity for reciprocal innervation of the gall bladder and sphincter. In support of this view, Bergh and Layne have shown that the human sphincter goes through its cycle even when the gall bladder has been removed.<sup>2, 4</sup> Secondly, Boyden and Rigler<sup>12</sup> have shown that the emptying of the human gall bladder is not inhibited by severe faradic excitation of the stomach and duodenum. Thirdly, Johnson and Boyden<sup>11</sup> have shown that even in cats—animals in which it has been proved that the vagi accelerate evacuation of the biliary tract by increasing the tone of the gall bladder and by diminishing that of the sphincter—even in such animals egg yolk still causes emptying of the gall bladder after section of both vagi. Finally, Bergh<sup>14</sup> has shown that the human sphincter does not respond significantly to cholinergic or adrenergic drugs.

The existing evidence, therefore, favors the view that in man the gall bladder and the sphincter react independently to a given hormone in the blood stream, the one by contracting, the other by relaxing; and that the tone of the sphincter is maintained by its local nerve net. Perhaps this explains why it has not been possible as yet to relieve spasms of the sphincter unless antispasmodic drugs are employed—substances like amyl nitrite and nitroglycerin which act directly on smooth muscle—or such hormone-producing substances as  $MgSO_4$  and egg yolk.

#### SUMMARY

1. Magnesium sulfate is an effective agent in evacuating the human biliary tract, but is inferior in this respect to egg yolk. Thirty cubic centimeters of a saturated solution introduced directly into the duodenum induces, within 30 minutes, an average decrease of 42 per cent in the volume of the gall bladder and lowers the sphincter resistance 3 cm. of water (manometer reading). In the same interval egg yolk lowers the gall bladder volume 71 per cent and the sphincter resistance 7 cm.

<sup>6</sup>One reason why it is not considered to be a reflex inhibition of the gall bladder is that reflexes from the stomach and duodenum to the gall bladder cannot be demonstrated in man (Boyden and Rigler)<sup>12</sup> as in animals (Birch and Boyden).<sup>13</sup>

2. Magnesium sulfate acts upon gall bladder and upon sphincter in the same way and for the same length of time as egg yolk. It differs only in degree, a characteristic which may be attributed to slower absorption rate or less effective chemical action. Accordingly, it is suggested that magnesium sulfate, like egg yolk, is to be considered as a hormone-producing substance which acts independently, through the blood stream, upon both the gall bladder and the sphincter of Oddi.

3. The two end organs, however, react differently to a given stimulus. Initially, a dose of either egg yolk or magnesium sulfate usually causes the sphincter to contract. This, in turn, may interrupt the contraction of the gall bladder which is just getting under way, thereby producing the so-called "two-minute pause." By the end of the first 4 or 5 minutes, however, the sphincter enters a period of progressive relaxation which lasts for an average period of 17 minutes. Meanwhile, the gall bladder begins its main phase of contraction which lasts for an average period of 30 minutes. Evidence from animal experimentation suggests that the reason why the hormone acts upon the sphincter for a shorter time than upon the gall bladder is that during fasting the tone of the sphincter is maintained by a local nerve net which has a higher threshold than that of the gall bladder.

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## PERFORATIONS OF THE GALL BLADDER OCCURRING IN A GENERAL SURGICAL PRACTICE IN A MODERATE-SIZED COMMUNITY

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NIEMEIER<sup>1</sup> in an article on the subject of perforations of the gall bladder separated the varieties of perforation as follows: (1) Perforation with communication with another viscus; (2) perforation with formation of a pericholecystic abscess, and (3) acute free perforation. Of the latter he cites one case with recovery. To these should be added external rupture of the gall bladder because of a case reported by Doran<sup>2</sup> in which an empyema of the gall bladder ruptured externally and established a fistula through which stones passed. X-ray visualization demonstrated an external biliary fistula.

Of the first type in Niemeier's classification, Jaffe<sup>3</sup> reported a case with rupture into the duodenum, followed by obstruction of the intestine by a large gall stone. In another case<sup>3</sup> two communications were present, one into the transverse colon and the other into the duodenum. In another case<sup>3</sup> the perforation was found to be into the liver. In two of our cases there were perforations into the liver and since there appeared to be considerable difference clinically between these cases and those which perforate into another organ, they should probably be classified separately. Therefore, to recapitulate, perforations of the gall bladder should be classified under five general types:

(1) Perforation with communication with another viscus; (2) perforation with formation of a pericholecystic abscess; (3) acute free perforation; (4) perforation into the liver; (5) external perforation.

The etiology of gall bladder perforations is essentially that of cholecystitis and cholelithiasis, plus some other factor, or factors, which are not established. There was no correlation in our cases between any predisposing or bodily factors and perforation, unless it was the age of the patient. With one exception, all were over 56 years of age. The incidence in our practice seems relatively high, namely, six cases in five years. Three other surgeons in this community have seen, respectively, two, one, and two cases in many more years. One of them also saw a case of perforation caused by an ice pick which had been thrown at the patient. The incidence in the New York Hospital as stated by Hotz<sup>4</sup> was 115 perforations out of 3,880 operations on the gall bladder,

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or 3 per cent. At the Mayo Clinic, Judd and Phillips<sup>5</sup> reported sixty-one cases in ten years. Eliason and McLaughlin<sup>6</sup> stated that the general incidence was found to be approximately from 1 to 3 per cent of all cases of biliary diseases.

Many facts are known regarding the pathogenesis of gall bladder disease, since it is fairly common and has been recognized for many years. It is doubtful that perforation of a normal gall bladder ever occurs, except from outside trauma. And, of the diseased gall bladders, many are found sterile upon culture, so it is probable that infection is secondary. Graham and Peterman<sup>7</sup> seem to have established the origin of the infection factor as lymphatic extension from neighboring viscera. The original damage is probably brought about by a combination of several factors, which can be summarized in the following paragraphs.

Cole, Novak, and Hughes<sup>8</sup> demonstrated in dogs that chronic partial obstruction of the gall bladder would cause inflammatory changes, but not necessarily bacterial inflammation. They produced surgically a flap of mucosa at the junction of the cystic duct with the gall bladder, the result of which was a "strawberry gall bladder" after varying lengths of time. Womack and Bricker<sup>9</sup> reported a method of experimental production of acute cholecystitis. They withdrew normal bile from normal dogs' gall bladders, concentrated it 50 per cent by evaporation, and reinjected it into the gall bladder after first tying off the cystic duct. Varying degrees of acute inflammation were found at autopsy. Cultures from some of the more acutely inflamed organs were often found to be sterile. Controls, using normal saline solution to reinject into the gall bladder, were in every case negative, since the gall bladders remained unaffected. Therefore, in their experimental animals, acute cholecystitis resulted from an occlusion of the cystic duct with concentration of the occluded bile. Hellwig,<sup>10</sup> however, feels that it is very possible that, during the manipulations inherent in the experiment, reflux of pancreatic juice may have occurred. The admixture of trypsin with bile thus resulting may have been responsible for the changes that occurred, somewhat in the manner of the production of acute pancreatitis.

Glenn and Moore<sup>11</sup> recently reported twenty-five cases of perforation of the gall bladder. In their cases rupture into the liver was most common. They found in every case evidence of formation of Rokitsky-Asehoff sinuses and ascribed rupture to the formation of these sinuses. These structures are small outpouchings of the gall bladder mucosa into the muscularis, caused by increased intracystic pressure and weakening of the wall by inflammation. Jaffe<sup>3</sup> definitely ascribed rupture in one case to decubitus ulceration by a stone causing pressure necrosis in the neck of the gall bladder.

In the six cases here presented the constant symptom was pain in the gall bladder region, usually very severe, but not diagnostic of perforation. There was usually nausea and vomiting, and sometimes jaundice. The onset was usually acute, but not necessarily cataclysmic.

but no rigidity. The urine was negative, W.B.C. was 13,600, and Hb 87 per cent. X-ray reported nonvisualization of the gall bladder. For six days she was treated conservatively and on August 1, was operated upon. At operation there was found empyema of the gall bladder, with many small stones, rupture into the liver with formation of an abscess cavity containing stones, and many adhesions. Funduscotomy was done, drains placed, and the ducts left unexplored. She had a very stormy course, running a septic temperature until death occurred August 13, on the twelfth postoperative day. Post mortem showed a generalized peritonitis with a small liver abscess and purulent cholangitis.

*Comment.*—This was another case of perforation into the liver. It would seem better to operate in the first twenty-four hours after the onset of acute gall bladder symptoms where there is fever and increased leucocyte count, for delay is often fatal, enough so as to overshadow the mortality of early operation.

*CASE 3.*—A woman, aged 60 years, was admitted Dec 1, 1940, complaining of severe pain in the region of the gall bladder, not relieved by morphine, and present for one day. For fifteen years she had had dyspepsia and bloating, and for six years colicky attacks, with a great deal of intermitting gastric symptoms. She had never been jaundiced, however. On examination her temperature was found to be 97° F, pulse 100, and respirations 35. Tenderness and rebound tenderness were marked throughout the abdomen, more in the gall bladder area. There was generalized rigidity. The urine was negative, the W.B.C. 4,770 with 78 per cent polymorphonuclears, and Hb. 91 per cent. The Wassermann was reported as negative. A scout film of the abdomen showed no stones, no distended loops of bowel, and no air over the liver. At operation, two hours after admittance and twenty four hours after the onset of the pain, free bile was found covering all the peritoneal surfaces and in considerable quantity. The gall bladder was full of stones, and the proximal third was gangrenous, with a large free perforation near the neck. Cholecystectomy was done and the abdomen closed with drainage. The course was uneventful and she was dismissed after twenty days. The pathologist reported chronic cholecystitis with stones.

Because of the acuteness of the symptoms, rather than the fact that the patient presented a "gall bladder" picture, she would have been operated upon by any surgeon who might have seen her. It is such cases that impress us with the desirability of early operation upon the acute gall bladder.

*CASE 4.*—A man, aged 78 years, was admitted Aug 21, 1941. He had an acute onset of very severe pain in the abdomen, followed by nausea and vomiting. The pain was so severe he was unable to move. During eight hours he was watched, with the possibility of coronary thrombosis in mind. His temperature was 96° F, pulse 100, and blood pressure 180/100. There was no jaundice. Boardlike rigidity was present throughout the abdomen, with marked tenderness and rebound tenderness. The W.B.C. was 12,800, with 66 per cent polymorphonuclears, and Hb of 16.9 Gm. A flat plate of the abdomen was negative. The patient had had two similar attacks of lesser severity in the last five years. At operation, about ten hours after onset, there was found free bile in the abdomen, a few adhesions about the gall bladder, and gangrene with perforation of the gall bladder. The gall bladder was contracted and contained several small stones. Partial cholecystectomy was done, leaving a drain in the neck. The pathologist reported acute cholecystitis with cholelithiasis. The patient immediately ran a very high temperature, which increased for four days, during which time he was irrational. He died on the fourth



postoperative day. At post mortem the heart, lungs, and kidneys showed nothing to account for death, and the liver was about normal.

The above patient was operated upon even earlier than the one previously cited, but died. The course was very suggestive of the "liver death" of Heyd.

CASE 5.—A man, aged 56 years, was admitted Feb. 26, 1942, complaining of cramps in the abdomen and gas on the stomach. There was a past history of indigestion, pain in the upper abdomen, nausea and vomiting for some years, and a gastroenterostomy two years previously. On examination, nothing much was found but the scar from his operation. The urine was negative, W.B.C. 6,600, Hb. 75 per cent, and Wassermann negative. Stomach x-rays were negative, other than confirming the gastroenterostomy. The gall bladder was not visualized with the dye. He was put on a modified Sippy regime until March 4, when he began having pain in the gall bladder region, nausea and vomiting. For four days he ran a temperature between 100 and 101° F., with a white blood count averaging 10,000. He improved until March 21, when operation was performed because of a sudden accession of pain and tenderness. At operation there was found free bile and free stones in the peritoneal cavity. There were many adhesions about the gall bladder, but the perforation was not found. A cholecystectomy was done and a large quantity of bile was drained. Progress was fairly good until the sixteenth postoperative day, when he signed a release and went home, still with some bile drainage from the wound.

This case is similar to the one cited by D'Abreon<sup>13</sup> and is unusual in that the treatment he was on is also that recommended for gall bladder disease, that is, small frequent feedings to avoid overstimulating the emptying reflex, but at the same time causing repeated minimal stimuli in order to keep a constant flow of bile into the duodenum. He was also on bed rest and received sedatives and antispasmodics.

CASE 6.—A young man, aged 23 years, was admitted Jan. 21, 1942, complaining of severe pain in the abdomen, nausea and vomiting, and a mass in the right side of his abdomen. These had been present four weeks, following an acute onset. In the meantime, he noticed some relief from warm moist compresses. He said that for five years he had been under treatment for ulcers. On examination, he was very tender and rigid in the region of the gall bladder and a very hard fixed mass could be felt in the gall bladder area. The urine was negative, W.B.C. 13,700, with 60 per cent polymorphonuclears, Hb. 12.8 Gm., and a red count of 4,000,000. Chest x-ray and a scout plate of the abdomen were negative. On January 24, three days after admittance, he was operated upon. There was an inflammatory mass which included abdominal wall, duodenum and colon, and lower border of the liver. In the center of the mass was an almost destroyed gall bladder with a liver abscess communicating with it. There were no stones. The remnants of the gall bladder were surrounded by a thin layer of purulent material. With considerable difficulty, the whole mass was removed. The pathologist reported ulcerative cholecystitis and chronic hepatitis. The patient's course was uneventful until February 5, when he developed small bowel obstruction and an enterostomy was performed. His condition was improved until February 24, when he had massive hemorrhages from the mouth and bowels and died. At post mortem, fresh blood was observed in the cecum, duodenum, and stomach, but the sources of the hemorrhages could not be determined. There was a chronic, indurated duodenal ulcer, but with no evidence of recent hemorrhage and no evidence of perforation.

This apparently was a case of perforation of the gall bladder, with

large here, as it does in all cases of gall bladder disease, and liver damage may be said to be the deciding factor in the surgical mortality of gall bladder disease. We are impressed over and over again with the necessity of considering the liver first of all in our gall bladder surgery. We are often reminded, also, of the frequent occurrence of gall bladder disease accompanied by chronic peptic ulcer and appendicitis, as Moynihan pointed out years ago.

In presenting these six cases, we were partly motivated by the desire to hold up examples of surgical procrastination. All the patients should have been operated upon much earlier (except in Case 2), when liver damage was minimal.

The advantages of early operation in perforated gall bladder disease are just as applicable to acute cholecystitis before perforation occurs. These advantages are that minimal liver damage is present, the lymphatics are sealed by inflammatory edema and exudate, the peritoneum is in a state of acute vaccination reaction, adhesions are not established, the planes of dissection are easily found and separated, often because of marked perieystic edema, and, finally, in case perforation has not occurred, a surgical catastrophe has been prevented.

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## AN EXPERIMENTAL STUDY OF METHODS FOR CLOSING THE DUODENAL STUMP AFTER GASTRIC RESECTION

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THE reported operative mortality for gastric resection varies from 5 to 26 per cent.<sup>1</sup> Leakage from the duodenal stump leading to peritonitis is the major cause of death, according to Moynihan and Perelman.<sup>2</sup> The importance of proper closure of the duodenal stump in the Polya-Reichel or Hofmeister-Finsterer types of Billroth II partial gastrectomies is appreciated by surgeons, but critical evaluations of the various methods now employed have been sparse.

The Kerr-Parker procedure for closing the duodenal stump is the one recommended by the most recent American texts of operative surgery.<sup>3</sup> In this method, the duodenum is crushed with a clamp and sectioned flush with the proximal side of the clamp. A continuous Cushing seromuscular suture is then inserted which inverts the edges when the clamp is withdrawn and the suture pulled taut. A second row of seromuscular sutures serves to reinforce the closure. Several special clamps such as the Clute modification of the Furniss clamp<sup>4</sup> have been recently introduced to facilitate the duodenal closure, but their use also necessitates some duodenal crushing.

The procedure popularized by Doyen<sup>5</sup> is the one found in the older texts of operative surgery.<sup>6</sup> The duodenum is crushed with a clamp which is replaced by a ligature, then sectioned proximal to the ligature, and the stump inverted with a purse-string suture. This method requires the mobilization of a large area of duodenum, a procedure frequently rendered difficult by the retroperitoneal attachments of the human duodenum, especially when the latter is the site of an ulcer.

Von Haberer recommends the open method in which no clamps are used. The duodenum is sectioned, the distal end closed with a continuous Connell suture, and a second row of continuous seromuscular sutures inserted.<sup>7</sup> Lahey prefers this method, but only because it does not waste as much duodenum as the Kerr-Parker closure. He states that if the edges are crushed first with a clamp, a better result is obtained.<sup>8</sup> Steinberg, on the other hand, believes that it is not advisable to use crushing clamps on the duodenal stump because clamps crush and devitalize tissue and thus jeopardize successful closure.<sup>9</sup> Both Lahey and Steinberg recommend fine chromic catgut for the first row of sutures, and the silk for the second row.

Perelman, using ten dogs to study duodenal closure, concluded that the Kerr-Parker method gave the best results. He states that the more firmly the bowel is crushed, the better the stump will heal, and that the purse-string method gave the poorest stump. His opinion of the condition of the stump postoperatively was based solely upon gross and microscopic examination.

The object of this experiment was to perform gastric resections on a large series of dogs, evaluate the three fundamental types of duodenal closures by means of a quantitative method, and thus develop a "base" for comparison in future studies.

#### METHODS

Gastric resections were performed on ninety-six dogs. The duodenum was closed with chromic twenty-day 000 Armour's catgut in seventy-two animals, and with silk in the remaining twenty-four. The dogs were divided into four series of twenty-four each, according to the types of closure which were:

Series I. Von Haberer open method without clamps or crushing (catgut).

Series II. Crushing clamp method of Kerr-Parker (catgut).

Series III. Simple ligature followed by purse-string method without clamps or crushing (catgut).

Series IV. The same procedure as in Series III except that Size A black silk twist (Belding Corticelli) was substituted for catgut.

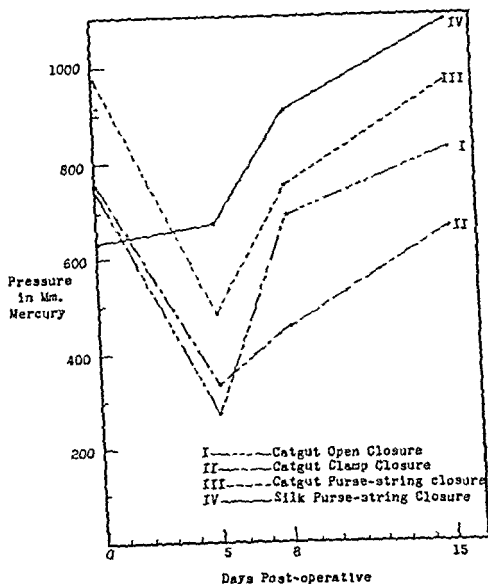
Horsley and others have emphasized that back pressure in the duodenum after Billroth II operations leads to separation and leakage.<sup>10</sup> For this reason we decided that the best method for measuring the strength of the duodenal closure would be to determine the air pressure necessary to blow out the stump. This was done by sectioning the duodenum at its distal untraumatized end, inserting a glass tube which was then tied in place, and connecting the tube to a bicycle pump through a specially constructed, large mercury manometer. The intraluminal pressure of the duodenum could thus be increased until rupture occurred, at which moment the pressure reading on the manometer was noted.

Each series of twenty-four dogs representing one type of closure was subdivided into four groups of six dogs each. In the first group of each series, the duodenal stump was blown out at the conclusion of the operation; in the second group this procedure was carried out on the fifth postoperative day, and in the third and fourth groups, on the eighth and fifteenth postoperative day respectively.

#### RESULTS

Table I shows the average pressures required to "blow out" the duodenal stump at the selected postoperative intervals. These figures have

been graphed in Fig. 1 to facilitate interpretation of results. The curves of all the catgut closures follow a similar pattern. The resistance to pressure falls to the lowest point on the fifth postoperative day, after which it rises steadily so that by the fifteenth postoperative day it is almost the same as immediately after the operation. The silk closures, however, show no postoperative drop but progressive increase in the resistance of the stump from the day of operation to the termination of the experimental observation period.



Statistical studies were made on all our data because the variations within a group may be as large as the difference between the means of any two groups. Significance was determined by using Fisher's formulas and tables as given in his book on statistical methods, pages 128 and 177.<sup>11</sup>

The results of this statistical analysis are shown in Table II. Study of our results show that:

1. The ligature and purse-string type of closure is the strongest, for only on the eighth postoperative day does any other procedure (open method) come close enough to eradicate any significant difference.
2. The open (Von Haberer) and clamp (Kerr-Parker) types of closures have the same strength immediately after the operation and on the fifth postoperative day. On the eighth postoperative day, the open method is significantly stronger than the clamp method, and on the fifteenth, slightly so.
3. The silk purse-string closure is much weaker than the catgut purse-string closure immediately after the operation, but slightly stronger at all subsequent times.

TABLE I  
PRESSURES REQUIRED TO "BLOW OUT" DUODENAL STUMP

	GROUP 1. IMMEDIATE P.O. PRESSURE TEST	GROUP 2. FIFTH DAY P.O. PRESSURE TEST	GROUP 3. EIGHTH DAY P.O. PRESSURE TEST	GROUP 4. FIFTEENTH DAY P.O. PRES- SURE TEST
Series I. Catgut Open Closure (Von Haberer)	740*	275	689	826
Series II. Catgut Clamp Closure (Kerr-Parker)	755	329	458	662
Series III. Catgut Purse-string Closure (Modified Doyen)	982	486	750	962
Series IV. Silk Purse-string Closure (Modified Doyen)	629	675	904	1091

\*Each number represents mean of pressures for six dogs, expressed in mm. mercury.

TABLE II  
SIGNIFICANCE OF CATGUT

<i>Immediate—Between:</i> Open and clamp —No significance Open and Purse- —Slight significance string Clamp and purse- —Significant string	<i>Fifth Postoperative Day—Between:</i> Open and clamp —No significance Open and Purse- —Significant string Clamp and purse- —Significant string
<i>Eighth Postoperative Day—Between:</i> Open and clamp —Significant Open and Purse- —No significance string Clamp and purse- —Significant string	<i>Fifteenth Postoperative Day—Between:</i> Open and clamp —Slight significance Open and Purse- —Significant string Clamp and purse- —Significant string
<i>Between Silk and Catgut Purse-String Method:</i> Immediate —Significant Fifth postoperative day —Slight significance Eighth postoperative day —Slight significance Fifteenth postoperative day —Slight significance	

#### CONCLUSIONS

1. In the closures employing catgut as suture material, the ligature and purse-string method (without the use of clamps) is the procedure which gives the strongest closure of the duodenal stump. In the human being, however, anatomic and pathologic considerations may frequently render this procedure impractical, and a choice must be made between the other two methods.

2. The open method of Von Haberer is preferred to the clamp closure of Kerr-Parker because between the fifth and eighth postoperative day (the period of greatest postoperative mortality) the duodenal stump in the clamp method shows much less resistance to intraluminal pressure.

3. Silk ligature followed by the silk purse-string method was found stronger than catgut after the first postoperative day. The trend toward using silk in closure of the duodenum is supported by our results.

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TABLE I

PRESSURES REQUIRED TO "BROW OUT" DUODENAL STUMP

	GROUP 1. IMMEDIATE P.O. PRESSURE TEST	GROUP 2. FIFTH DAY P.O. PRESSURE TEST	GROUP 3. EIGHTH DAY P.O. PRESSURE TEST	GROUP 4. FIFTEENTH DAY P.O. PRES- SURE TEST
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<i>Eighth Postoperative Day—Between</i> Open and clamp —Significant Open and Purse —No significance string Clamp and purse —Significant string	<i>Fifteenth Postoperative Day—Between</i> Open and clamp —Slight significance Open and Purse —Significant string Clamp and purse —Significant string
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## CONCLUSIONS

1 In the closures employing catgut as suture material, the ligature and purse string method (without the use of clamps) is the procedure which gives the strongest closure of the duodenal stump. In the human being, however, anatomic and pathologic considerations may frequently render this procedure impractical, and a choice must be made between the other two methods.

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3. Silk ligature followed by the silk purse-string method was found stronger than catgut after the first postoperative day. The trend toward using silk in closure of the duodenum is supported by our results.



joint are the most important factors, it always is necessary to proceed with a clear conception of the mechanical features of contracture, of the normal function of the knee joint, and of the relation of the anatomic structures which may block extension.

Both Silver<sup>3</sup> and Wilson<sup>4</sup> have stressed the role of the capsule, as well as the flexor muscles, in the deformity, and their operative procedures have been directed primarily to these structures. An outstanding feature of our own experience has been that many of the severe flexion deformities, particularly in atrophic arthritis, can be corrected at operation by releasing contracted structures other than the posterior joint capsule. When the marked contracture of the deep popliteal fascia is completely resolved, a major portion of the deformity is overcome. This experience coincides with that of Kulowski<sup>5</sup> who stated that among the many tenotomies performed at the University of Iowa Clinic, surprisingly few cases required additional capsuloplasty. He pointed out that "fortunately the capsule is the last structure to take part in the contracture and that posterior capsular shrinkage does not occur in myogenetic contractures unless a very long period has elapsed."

The structures of the knee joint are meagerly described in the standard works on anatomy, and hence we are indebted to Normand L. Hoerr,<sup>6</sup> professor of anatomy of Western Reserve University Medical School, for the following description. "The deep fascia of the popliteal region is a direct continuation of the fascia lata of the thigh, and over the popliteal fossa it is sometimes thin but always possesses considerable strength, owing to the numerous transverse fibers which are interwoven with longitudinal fibers. This deep fascia, which can be called popliteal fascia proper, is firmly attached on each side to the tendons of the muscles which bound the popliteal fossa; that is, the hamstrings above, and the plantaris and gastrocnemius below. The deep fascia is directly continuous with the connective tissue sheaths of the various muscles forming the boundaries of the popliteal fossa. The popliteal artery, popliteal vein, and sciatic nerve are held together by a sheath of fascia which is sometimes membranous, but often quite loose and containing considerable fat. Below the broad sheet of deep fascia which forms the roof of the popliteal space, the fascia becomes much looser and affords a fatty packing of the entire popliteal space. The floor of the popliteal fossa is formed from above downwards by (1) the popliteal surface of the femur, (2) the capsule of the knee joint, and (3) the strong fascia which covers the popliteus muscle. The resistant fascia roofing the popliteal fossa unites with the tendons and muscles, forming the walls of the space, and covers a well-delimited cavity, incapable of great distension." (Fig. 1.)

As Kulowski has explained, "the position of contracture is dependent upon the normal mechanics of the knee and follows definite physical laws. The key to the contracture complex is the flexion position. The associated elements are secondary phenomena directly dependent upon

# THE TREATMENT OF FLEXION DEFORMITIES OF THE KNEE

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WITH our hospital facilities strained to the utmost because of hospitalization insurance and the present military emergency, it behooves us to rehabilitate as many patients incapacitated with chronic arthritis as possible, at least to the point where they are not bedridden. Our municipal and county hospitals have many beds filled with patients who cannot be removed because of flexion deformities of the knees, so their treatment becomes a social and economic, as well as a medical problem.

It may be well to review some of the facts regarding these cases, and to stress the importance of a conservative point of view in dealing with them. As orthopedic surgeons, our interest in the problem pertains largely to correction, but we also know that many flexion deformities of the disabling type can be prevented, with attention to rest and maintenance of the proper position of the joints during the inflammatory stage of arthritis. Swaim<sup>1</sup> and others have stressed that this is the crux of the problem of preventing arthritic deformities, which are always flexion deformities and develop while the patient is in bed. With the ever increasing cooperation between medical men and orthopedic surgeons in treating arthritis, we may all do our share in the prevention of severe flexion deformities.

Flexion deformities of the knees may result from a variety of conditions, including spastic paralysis, poliomyelitis, fractures and other injuries, and tuberculosis, but the vast majority of cases is due to chronic arthritis of the infectious, rheumatoid, or atrophic type.

Haggart<sup>2</sup> has classified flexion contractures of the knee as follows: (1) arthrogenic, the result of a disturbance in the joint itself, usually rheumatoid or atrophic arthritis; (2) neurogenic, in which there is fixation brought about by contracture of a muscle or muscle group as a result of abnormal innervation; (3) myogenic, which may be paralytic as the result of muscular imbalance after poliomyelitis, or myositic, resulting from inflammatory processes in the adjacent muscles, particularly the hamstring group; (4) congenital, usually associated with flexion contractures elsewhere in the body; and (5) static, consequent on hip flexion, short gastrocnemius, or faulty posture.

Although each case of flexion deformity must be considered as an individual problem, in which the patient's general condition, age, length of disability, and the degree of involvement of the various tissues of the

is no hope of restoring a functional joint, surgical treatment is useless. In polyarthritis, we have found to our dismay in one or two instances that the patient should not be subjected to surgery unless he is able to use his upper extremities well enough to aid himself in getting in and out of bed. Aged patients and those whose general condition make them poor operative risks also should not be subjected to a corrective procedure.

When patients have been properly selected with these factors in mind, it then becomes important to determine the extent of involvement of the joint structures, and consequently the type of treatment necessary. The procedure in most cases must be surgical release of the contracted tissues, followed by mechanical procedures to increase extension

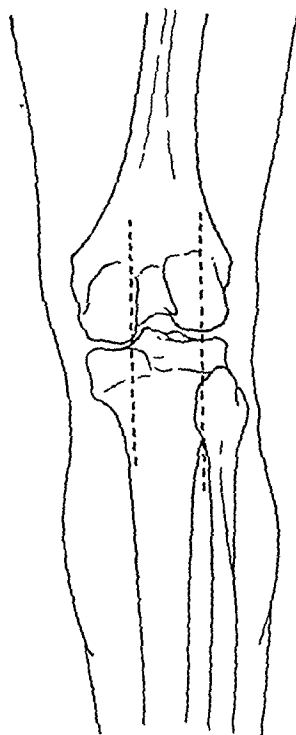


Fig. 2A.

Fig. 2. A and B.—Lateral and medial incisions of the knee.

of the joint. Closed methods, such as manual manipulation and the application of traction are satisfactory only in the mildest cases, but one should not hesitate to use them when they will suffice. In the majority of instances, the problem becomes one of deciding the extent of surgical correction which will be necessary.

It is difficult, if not impossible, to determine by diagnostic means whether the contracture is extra-articular or intra-articular. Kulowski

it. The contracture position is therefore a fixed exaggeration of the normal flexion, incident to the newly established muscular equilibrium, and is certainly not a haphazard event."

In any attempt at correction of a flexion deformity of the knee, the treatment must be planned to take into consideration the nature and extent of the underlying disease process and the tissues which are actually involved in the contracture; the mechanical devices used to aid in extension must be applied with attention to the physical laws which govern the function of the joint.

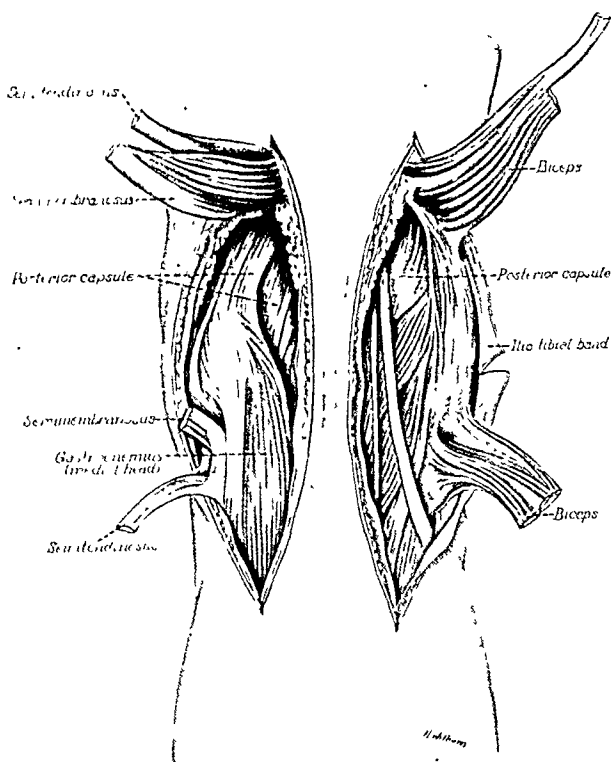


Fig. 1.—Posterior compartment of the knee joint with the deeper structures exposed, showing the popliteal fascia extending around the gastrocnemius muscle and between the muscle fibers.

The first consideration in the treatment of flexion deformities of the knee is a careful selection of cases. Surgical procedures are contraindicated in the presence of an inflammatory condition of the joints. The advice of an internist or someone particularly interested in the treatment of arthritis should be sought in all cases in which there is any question of continued activity of the disease process. When there is joint destruction so severe that ankylosis will certainly result or there

nerves and arteries. One after another of the layers of tissue are divided, depending on the results. If the hamstrings have been divided without releasing the contracture, then the popliteal fascia is thoroughly exposed and divided, even that portion which forms the intramuscular septa. In most instances it also is necessary to separate the heads of the gastrocnemius. This proves sufficient in the majority of cases and it is not necessary to do a capsuloplasty.

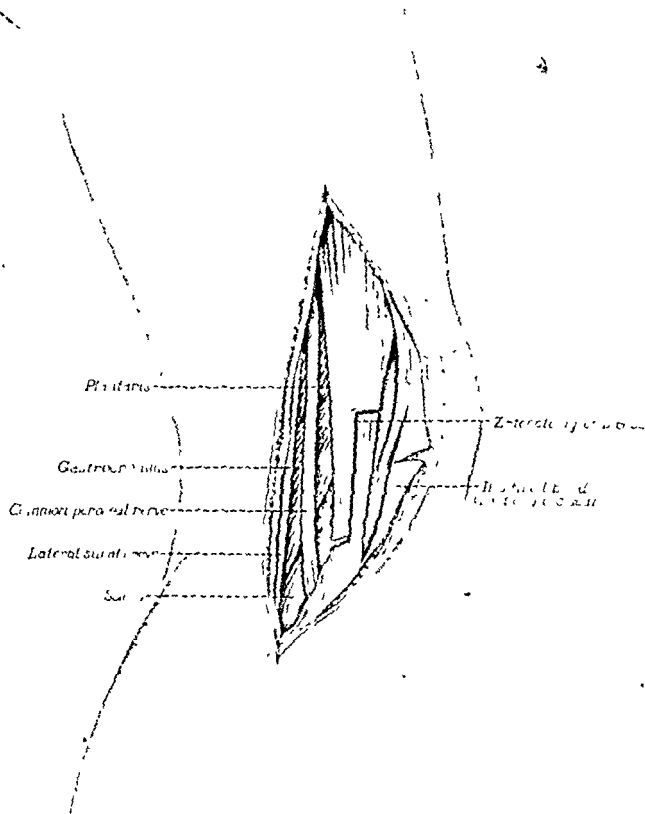


Fig. 3—Lateral incision showing tenotomy of the biceps tendon, incision of the iliotibial band and exposure of the peroneal nerve.

In those cases in which fasciotomy is ineffective in releasing the contracture, a capsuloplasty is performed, according to Wilson's technique. In atrophic arthritis, where there usually is marked osteoporosis, sharp dissection is preferable to periosteal stripping. If the flexion deformity is not completely overcome by this procedure, we agree with Silver that the knee should not be forcibly extended, because of the danger of fracture, of subluxation, of exacerbation of inflammation, and of injury to the nerves and arteries. The warning frequently has been sounded

has stated that the block due to capsular shrinkage can be determined clinically by the presence of a posterior springy resistance against passive extension of the knee in the presence of relaxed hamstrings. In our own experience, this finding has limited application because when there is intracapsular involvement the extracapsular structures, particularly the hamstrings, are also contracted, as a rule.

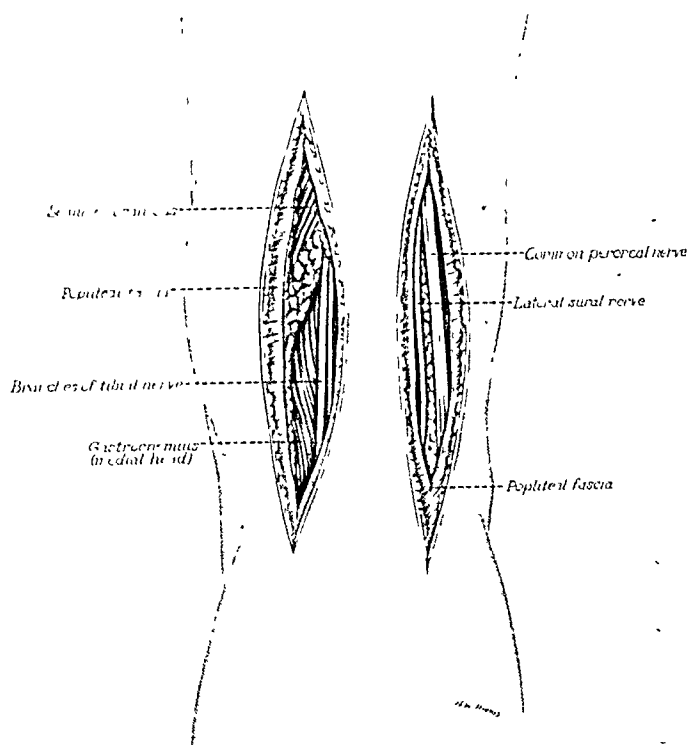


Fig. 2B.—For legend see page 749.

Hence the question of which tissues are contracted has to be answered at the operation, which should be undertaken with the idea that the procedure will be determined by the individual findings and will be as conservative as is consistent with good functional results. When the contracture is extra-articular, usually with flexion deformity of less than 45 degrees, tenotomy of the hamstrings ordinarily is sufficient. A lateral approach is made just medial to the biceps tendon over the course of the peroneal nerve. The medial incision is slightly to the inner side of the midline of the popliteal space and the tibial nerve and branches (Figs. 2, 3, and 4). This gives a thorough exposure of the posterior portion of the knee and at the same time brings into view the popliteal

ankylosis of the joint is impending, osteotomy either above or below the knee joint to correct the deformity is the method of choice.

The operation is considered satisfactory when extension has been corrected to within 15 degrees of normal. Additional extension usually is secured by the postoperative application of traction and by physical therapy, consisting of heat, massage, passive exercise, and muscle setting. Our practice is to employ Russell traction for extension because that affords a certain degree of extension to the upper portion of the tibia while producing traction which eliminates a backward luxation of the tibia in the knee joint. Various other apparatus, based on similar mechanical principles, have been proposed to aid extension of the joint, so the type of traction used becomes a matter of individual choice. Skeletal traction has been advocated by a number of authorities, but we have not used it, largely because of the dangers involved in inserting a pin into atrophic bones, and because the methods used to increase extension have been satisfactory.

Synovial hypertrophy is common in cases of flexion deformities of the knees, particularly in those with intra-articular lesions. In a number of instances, it has appeared that this would be an obstacle to adequate extension of the joint, and plans have been made for a synovectomy following a period of rest and traction. However, in none of these cases has synovectomy proved necessary because the synovitis subsided satisfactorily during the postoperative period while the patient was at rest. Magnuson<sup>7</sup> also has noted that removal of the synovia has not been necessary in his cases subjected to joint débridement. In this connection, it is interesting that Steindler (as quoted by Kulowski<sup>8</sup>) has called attention to hypertrophy of the infrapatellar fat pad as a primary cause of flexion deformity and an anterior mechanical block to extension.

#### CONCLUSION

It is important to emphasize that the conservative viewpoint should be carried through to the evaluation of the results of treatment. In many instances, the patient cannot be rehabilitated to the extent that he regains normal function of the knee joint. But if enough function can be restored to enable him to move about, even with crutches, rather than to be completely bedridden, a great deal has been accomplished, both from the standpoint of the patient and from the standpoint of society.

Experience has shown that by keeping in mind the structure of the knee joint and the nature of the disease process resulting in flexion contracture, it is possible to rehabilitate these patients satisfactorily without resorting to the radical procedure of capsuloplasty in the majority of cases. When tenotomy does not suffice, fasciotomy does, as a rule, and except in the rare cases in which the condition is most advanced, the capsule may be left intact. These more conservative procedures naturally carry less risk of infection, increased stiffness and other

that excessive force applied in manipulation may cause postoperative fractures because of the atrophic condition of the bones. In some of Wilson's early cases in which complete extension was secured at operation, there was evidence of injury to the nerves. In later cases, he obviated this complication by taking care to free the nerve from the surrounding tissues for a considerable distance. In extreme contractures

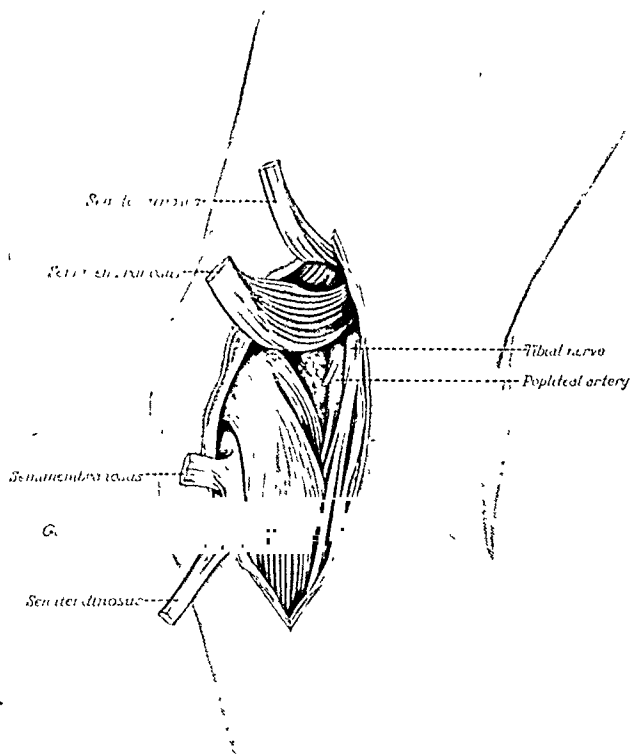


Fig. 4.—Medial incision showing semimembranosus and semitendinosus tenotomized tibial nerve and popliteal artery and inner head of the gastrocnemius exposed.

it must be remembered that the danger of injuring the nerves and vessels at operation is increased because they may be displaced from their normal positions or imbedded in scar tissue, making their identification difficult.

In those instances where tenotomy, fasciotomy, and capsuloplasty are contraindicated because of excessive flexion deformity, where these procedures may result in damage to nerves and blood vessels, or where



# CHRONIC EMPYEMA DUE TO DERMOID TUMORS OF THE MEDIASTINUM

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THE causes of chronicity in empyema thoracis have been listed as: inadequate drainage, presence of foreign bodies, communication with the lung, cavities that cannot be spontaneously obliterated, and tuberculosis or fungus infections. I should like to emphasize a sixth cause—dermoid tumors of the mediastinum.

Dermoid tumors of the mediastinum are called epidermoids when derived from ectodermal elements, true dermoids when there is in addition evidence of mesodermal derivation, and teratoma when derivatives of all three germinal layers are present.<sup>1</sup>

Secondary infection sometimes constitutes a deceiving as well as a dangerous complication of these neoplasms and leads to masking their presence behind the clinical syndrome of chronic empyema. Infection usually occurs from rupture into the neighboring pulmonary parenchyma or bronchi due to pressure. Suppurative pleurisy may result which, even when adequately drained, will not be permanently cured because of the underlying pathologic process. Since this fact seems to need emphasis, the following strikingly similar case histories are presented.

## CASE REPORTS

CASE 1.—J. B. is a young woman 28 years of age. In 1917, at the age of 3 years, she had what was diagnosed as pneumonia of the right lung with subsequent empyema which was treated by tube drainage. A sinus persisted which continued to discharge purulent material, despite which the patient remained quite well. This sinus was closed in 1923 when the patient was 12 years of age. For two years she coughed up the same type of material which had come from her external thoracic opening. She failed to improve during this time, so the tract was reopened in 1925. In attempts to eradicate what was thought to be a chronic empyema cavity, thoracoplastic procedures were carried out in 1928 and again in 1931. It was at this later time that sebaceous material and hair were found at a postoperative dressing of the wound. More of the same substance was removed and on three occasions radium was used to destroy the cyst wall without success. In 1932, a tumor was removed from the right chest weighing 292 Gm.; it contained bone, lymphoid tissue, stratified squamous epithelium, sebaceous glands, and connective tissue. In 1931, residual bronchial fistulas were closed successfully. Two years before removal of the thoracic tumor this patient complained of aching joints associated with swelling. Except for a continuation of this complaint to a lesser degree she is in good health. She has no symptoms referable to her chest, except slight dyspnea on exertion.

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complications, shorten the period of convalescence, and hence are distinctly preferable from the standpoint of patient, surgeon, and hospital.

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Fig. 4—Photograph of gross specimen of dermoid tumor surgically removed. Note the hair characteristic of these tumors.



Fig. 5.



Fig. 6.

Fig. 5 (Case 1).—Postoperative roentgenogram of chest. There is considerable thoracic deformity because the patient had been treated for chronic empyema for many years before diagnosis of tumor was made.

Fig. 6 (Case 2).—Roentgenogram of chest showing density in right lower median lung field, as in Case 1.



Fig. 1 (Case 1).—Roentgenogram of chest showing density in right lower median lung field.



Fig. 2.

Fig. 3

Fig. 2 (Case 1).—Lipiodol visualization of sinus tract. This and accompanying lateral view clearly demonstrate the anterior location of the lesion.

Fig. 3 (Case 1).—Lateral view of lipiodol visualization

ix years ago. In the summer of 1938, there developed, in addition to the productive cough, pain behind the sternum. A physician was consulted who found purulent fluid on aspiration of the right chest posteriorly. Tube drainage was instituted and was continued until July, 1939.



Fig. 19.—Low-power photomicrograph of tumor showing ectodermal and the adermal derivative.



Fig. 22.—Photomicrograph viewed with moderate deformity. This may be improved later by covering with the acetate.

CASE 2.—S. A. is 30 years of age. Although it is difficult to obtain a clear picture of her earlier complaints, there is definite evidence of some thoracic disorder associated with severe cough and expectoration of green, purulent sputum as early as



Fig. 7.



Fig. 8.

Fig. 7 (Case 2)—Anteroposterior view with catheter in sinus tract for lipiodol visualization. Notice oil in bronchial tree indicating the presence of fistula.

Fig. 8 (Case 2).—Lateral view of Fig. 7, which conclusively demonstrates the lesion to be in anterior mediastinum. Costovertebral gutter region is clear.



Fig. 9.—Photograph of tumor removed, showing hair on its surface.

dition to thorough general physical examination, specific investigation of the thorax must be carried out. The sputum and sinus discharges should be searched for tubercle bacilli, as well as for fungi of all types. Culture is made of both, as well as direct smear for hair, sebaceous material, cholesterol crystals, and epidermis. Guinea pig inoculation is advised.

Roentgen examination is made in both the anteroposterior and lateral views before and after the sinus is visualized by the injection of lipiodol or brominol. Fluoroscopy of the stomach and colon to rule out diaphragmatic hernia through the foramen of Morgagni is suggested. Wassermann and other tests for syphilis should be performed routinely. Aneurysm has been confused with tumor<sup>2</sup> and, of course, may lead to disaster if unrecognized. Bronchoscopy, and even endoscopic examination of the sinus, may confirm a tentative diagnosis if hair, cholesterol, etc., are found.

Characteristically, dermoids are found in the anterior mediastinum, extending laterally and posteriorly as they enlarge. A study particularly of the lateral roentgenograms of the chest in the cases presented shows the costovertebral gutter region to be free from disease. This is usually involved in a chronic empyema process. Lipiodol visualization of the sinus tracts demonstrates their extension into the anterior mediastinum. This suggests the diagnosis of dermoid tumor, which was further substantiated in each case by obtaining material from the sinus which was characteristic of these lesions, such as hair and sebaceous material.

At operation in each instance a tumor was removed. Hair can be seen on both specimens (Figs. 4 and 9). The derivatives of ectoderm and mesoderm can be seen on microscopic section (Fig. 10).

It is not the purpose of this paper to discuss the surgical treatment of mediastinal dermoids. Infection has been largely responsible for mortality in the reported operative deaths.

The surgical approach to each patient must be individualized. While the transpleural operation through a posterolateral incision as advocated by Harrington<sup>3</sup> affords the best exposure, and thereby facilitates careful dissection from other mediastinal structures, the anterior approach may be safer in the presence of infection. Because of the malignant changes in at least 15 per cent of these tumors, early surgical removal is advised.

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At this time she came to Presbyterian Hospital. Because she had a septic temperature the posterior sinus tract was opened more widely to promote adequate drainage. A tentative diagnosis was made of chronic empyema. Since her fever did not entirely subside, two months later a second operation was carried out to unroof the chronic empyema cavity. The sinus was found to extend far forward and at its anterior end a white movable mass was seen and felt. A piece of tissue was secured with a bronchoscopic biting forceps and histologic report was "sebaceous cyst." A diagnosis of anterior mediastinal dermoid was made. The

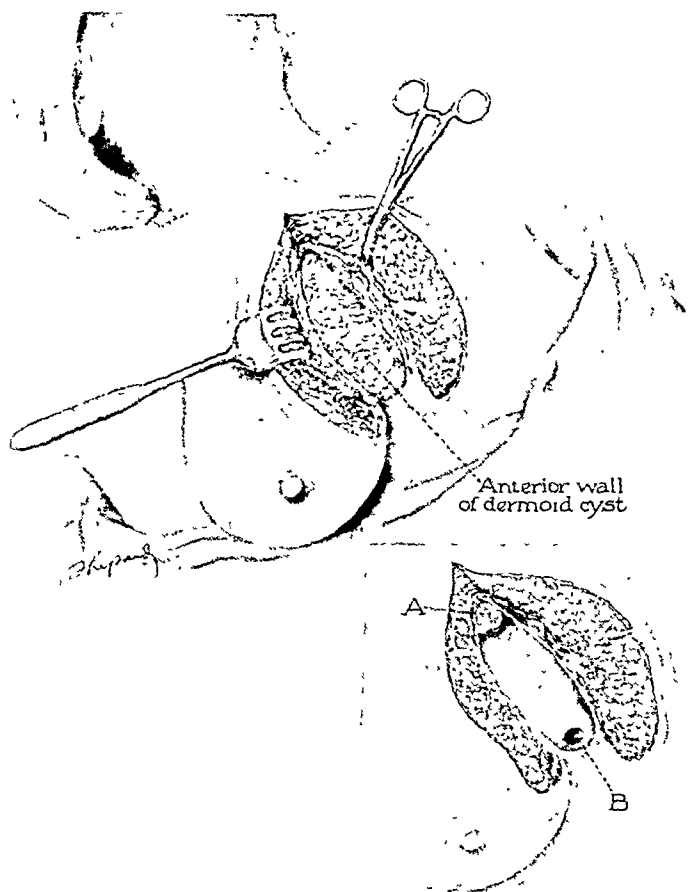


Fig. 12.—Upper illustration is that of the capsule surrounding the actual tumor. Within this was contained the purulent sebaceous fluid which drained from the posterolateral sinus whose anterior communication is shown at B; A marks the upper end of the tumor before its complete removal.

tumor was removed in two stages through an anterior thoracic approach. Since that time cholecystectomy has been performed for gallstones which were visualized in studying the thorax. These had produced severe colic on two occasions. The patient has gained twenty-five pounds in weight and is quite well.

#### DISCUSSION

It is only by carefully planned study that diagnosis of the underlying cause of chronic thoracic sinuses can be correctly made. In ad-



is by no means settled. Hypertrophic is redundant, for there is no other than hypertrophic kind of infantile pyloric stenosis. The latter term, that is, infantile pyloric stenosis (also employed in the title), appears to be the most precise. In German the equivalents of pylorospasm and pyloric stenosis are used interchangeably, while in English stenosis always denotes organic obstruction. The French, too, clearly distinguish between pylorospasm and pyloric stenosis, reserving the term *pseudostenose* for the former. The other Latin countries follow the French usage, while the Scandinavians and Central-Europeans copy the German example. In the older literature the designations of *stenosis pylori congenita* and *hyperemesis lactentium* are encountered.

In addition to these standard designations, one meets a host of loosely coined sporadic names, such as pyloric contracture, congenital pyloric spasm, essential pylorospasm, spastic stenosis, pylorostenosis, pyloric stenosis of infants, muscular hypertrophic pyloric stenosis, stenosing pyloric hypertrophy, and *maladie pylorique*.

#### HISTORY

Scattered accounts of cases closely corresponding to the entity now known as infantile pyloric stenosis were published as early as the seventeenth century. Kellett believes that the case report of Hildanus, a famous German pediatrician who flourished in the second half of the seventeenth century, should be accepted as an example of this disease; the date of the first description would thus be 1646. While this claim may be questioned, there is little doubt that the accounts of Blair (1717), C. Weber (1758), and Armstrong (1771) are strikingly characteristic of the disease as now recognized. The case observed by Hezekiah Beardsley has several distinctions: it appeared (1788) in the first medical periodical published in the United States; it was discovered and made public again by Sir William Osler; and for many years it was believed to be the earliest example of the disease then extant. In the early nineteenth century Pauli (1839) and Williamson (1841) made accurate independent observations of this condition, and Dawosky (1842) for the first time described the projectile character of the vomiting.

Considering the very typical clinical manifestations of the disease, the meagerness of the number of these reports is surprising and hardly explicable by the rarity of the disease alone. The very deplorable state of pediatrics, the general ignorance and even indifference in the matters of infant disease offer a more likely explanation. But even the few early reports made no impression whatever on contemporary medical thought. Children with hypertrophic pyloric stenosis continued to die with the disease undiagnosed and, what was more important, untreated. In fact, the original case reports were so completely covered with the dust of oblivion that they had to be rediscovered in the twentieth century, when the disease had long been well recognized in most of its aspects.

# Editorial

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## Recognition of Military Training as a Determination of Eligibility for American Boards

MANY of the younger men in the service have been concerned about the effect which the war would have upon their eligibility for the various American Boards. Whereas many men have previously outlined a course of formal surgical training which would make them eligible to take their respective board examinations, with the introduction of the United States into the war and the necessity of their enlistment in the Armed Forces, this formal training has necessarily been interfered with. It has been the hope of those interested in graduate medical training that recognition could be given for adequate training received in the Armed Forces.

It is significant that the American Board of Orthopedic Surgery, one of the oldest boards, has taken formal action concerning this. "In order that the committee on eligibility may have adequate data for evaluation of the training of applicants who have served with the Armed Forces, a plan will be set up whereby all who are assigned to orthopedic services will be provided with an orthopedic service record. These records must indicate the character and amount of orthopedic work performed at each post to which prospective applicants are assigned. The notations of each officer concerning his service at each post must be signed by his superior officer in charge of the orthopedic service and approved by the commanding officer. The orthopedic service record will be retained by the officer and finally will be submitted with his application to the Board for review by the committee on eligibility."

It is probable that other boards will follow the lead taken by the American Board of Orthopedic Surgery and set up similar plans because in this way it will be possible for the man getting adequate training to have this designated at the time he is getting it so that proper evaluation can be made whenever he makes application to take his examination. Because of the new ruling by the American Board of Orthopedic Surgery and because of the possibility of such a ruling being made by other boards, it is desirable that anyone contemplating taking examinations for the various boards should communicate with his respective board at the earliest possible moment in order that he may get information concerning the service record.

the changes of catarrhal gastritis frequently present as a secondary phenomenon. Inconsequential mucosal erosions may be found but true chronic ulcers have been described as great rarities (Kleinschmidt, and Thompson and Gaisford). The muscular coat of the entire stomach wall is also thickened to a lesser or greater degree and the lumen of the viscus may be considerably dilated. It is generally agreed that microscopically the increase in the volume of the pyloric musculature is due to a true hypertrophy; that is, there is an increase in the size of the component muscle cells without an increase in their number. (v. Mettenheim, on the other hand, states that the process is both a hypertrophy and a hyperplasia.) The inner, circular fibers are primarily involved, although the longitudinal layer also shows a lesser degree of similar alteration. The latter is usually  $\frac{1}{6}$  to  $\frac{1}{4}$  the thickness of the circular muscle coat (Balan) whose diameter, in turn, varies between 3 and 7 mm. (3 to 4 times normal) (Wollstein). While the connective tissue substance of the muscle coat also shows some increase in volume, this does not materially add to the formation of the pyloric swelling (as originally held by Hirschsprung, and Finkelstein and his associates).

Balan and later Cameron made the very significant observation that the elastic fibers of the submucosa and, to a lesser degree, of the muscularis mucosae and muscularis propria also partake of the process of hypertrophy and that this hypertrophy, together with the muscular hypertrophy, is limited to the pyloric canal (leaving the pyloric ring itself uninvolved) and is a progressive change, becoming more pronounced with the lengthening of the duration of symptoms, advancing in the long axis of the canal both orad and aborad.

The increase of muscle volume within the confinement of an adherent and unstretchable peritoneal covering transforms the limp and relaxed pyloric canal into a hard and solid tube. Another effect of the muscle swelling is the protrusion of the thickened pyloric segment into the duodenal lumen, much as the cervix intrudes into the vagina. The tension within the thickened pyloric muscular coat compresses the vascular branches and lends a pale, bloodless appearance to the component tissue. The consistency of the muscle turns *crisp and gritty*, but as the disease progresses, presumably on account of the stretching and loosening of the peritoneal covering by its growth, it again becomes softer and more vascular. It is this factor of age that apparently accounts for the two distinct types of pyloric tumor described by some authors (Heile).

There is a considerable body of evidence, based on observations in vivo, to show that the pyloric tumor undergoes a cycle of changes grossly visible and palpable. It apparently reaches its maximum hardness and size between the fourth and ninth postnatal weeks. Thereafter, it tends to become softer of consistency and smaller in extent (Higgins and Tallerman). Whatever the underlying cause, these cyclic alterations are in harmony with the modern views of pathogenesis and throw light

Thus when, in 1887, at the Wiesbaden meeting of the Gesellschaft für Kinderheilkunde, Hirschsprung described two cases of infantile pyloric stenosis, he in fact presented a new disease as far as the practitioners of medicine in attendance were concerned. Hirschsprung's interest was mainly in the anatomic aspect of the disease, his attention having been brought to the problem by the reports of Landauer (1879) and Mayer (1885) dealing with the pathology of hypertrophic pyloric stenosis in the adult. He gave an excellent account of the gross pathologic changes and expressed the supposition that these alterations were the cause of a definite clinical form of infantile vomiting. He further assumed that the adult type of hypertrophic pyloric stenosis originates from the infantile form—a question not yet answered even today. (See Elmer and Boylan, Frank, Judd and Thompson, McNamee, Rössle, McClure, Twining.)

Within a brief time after Hirschsprung's presentation the disease became widely known. The eagerness of the prodigiously growing medical science at the turn of the century quickly engulfed the new problem about which a large literature soon grew up. Finkelstein (first to describe the palpable pyloric tumor), Huebner and Pfaundler in Germany, Hutchinson and Thomson in England, and Holt, Downes, and Scudder in the United States, were especially eminent among those who early interested themselves in the disease.

*The Typical Clinical Picture.*—As a convenient reference, the picture of the disease as ordinarily manifested—an abstract model of the disease, so to speak—may be here given. The typical infant is a lusty male child, probably the first child of the family, born spontaneously after a normal prenatal development. He nurses well and shows good progress until his third week of life when, rather suddenly, he begins to vomit some of his feedings. While maintaining his appetite, and without developing a febrile disease, his vomiting becomes gradually more severe, he begins to lose weight, becomes wizened and, unless energetic medical attention intervenes, dies of starvation or pneumonia before reaching the age of three months.

#### PATHOLOGY

The pathologic anatomy of the disease is simple and clear-cut. All the essential alterations encountered are confined to the stomach and, in particular, to the pyloric canal (*canalis pyloricus sive egestorius*). The general wasting of the body and the pathologic processes developing terminally are secondary to starvation and in no way restricted to the disease.

The entire pyloro-antral region shows a shining, gray-white spindle-shaped thickening of cartilagenous consistency. The length of this swelling (loosely called tumor) is 2 to 3.5 cm. and its width 1.5 to 2 cm. with a wall thickness of 0.5 to 0.8 cm. Almost without exception (Arreger, Chiari, Rothschild, Wernstedt) the mucosa appears normal aside from

the changes of catarrhal gastritis frequently present as a secondary phenomenon. Inconsequential mucosal erosions may be found but true chronic ulcers have been described as great rarities (Kleinschmidt, and Thompson and Gaisford). The muscular coat of the entire stomach wall is also thickened to a lesser or greater degree and the lumen of the viscus may be considerably dilated. It is generally agreed that microscopically the increase in the volume of the pyloric musculature is due to a true hypertrophy; that is, there is an increase in the size of the component muscle cells without an increase in their number. (v. Mettenheim, on the other hand, states that the process is both a hypertrophy and a hyperplasia.) The inner, circular fibers are primarily involved, although the longitudinal layer also shows a lesser degree of similar alteration. The latter is usually  $\frac{1}{6}$  to  $\frac{1}{4}$  the thickness of the circular muscle coat (Balan) whose diameter, in turn, varies between 3 and 7 mm. (3 to 4 times normal) (Wollstein). While the connective tissue substance of the muscle coat also shows some increase in volume, this does not materially add to the formation of the pyloric swelling (as originally held by Hirschsprung, and Finkelstein and his associates).

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There is a considerable body of evidence, based on observations in vivo, to show that the pyloric tumor undergoes a cycle of changes grossly visible and palpable. It apparently reaches its maximum hardness and size between the fourth and ninth postnatal weeks. Thereafter, it tends to become softer of consistency and smaller in extent (Higgins and Tallerman). Whatever the underlying cause, these cyclic alterations are in harmony with the modern views of pathogenesis and throw light

upon the anatomic basis of the clinical observations that the disease, once past the first three months of life, shows an inclination to spontaneous healing.

The blunt projecting end of the hypertrophic pylorus creates certain anatomic relationships that are of practical importance. The apex of the fornix created all around this stopperlike mass and consisting of the duodenal mucosa becomes bound down to the muscular and serosal coats, forming the so-called "zone of adhesions" (Browne). Separation of the various layers at this point, therefore, becomes difficult and may cause technical mishaps at time of operation.

More recently degenerative changes of the plexus of Auerbach in the wall of the pyloric canal and stomach have been described (Herbst). The possible significance of this finding will be touched upon later.

#### ETIOLOGY AND PATHOGENESIS

The question of the causation of infantile pyloric stenosis has been a matter of extended speculation and has not as yet been accurately answered. In the following, the various known etiologic factors and the purely theoretic systems of pathogenesis, for the sake of clearer organization, will be discussed under separate headings.

#### ETIOLOGIC FACTORS

*Genetic (Hereditary) Factor.*—Genetic research in cases of infantile pyloric stenosis is only at its very beginning but already a considerable body of observations has been accumulated.

The most commonly appreciated evidence of heredity in a disease is its familial occurrence. Infantile stenosis was observed to occur in two siblings by Bousquet, Carstens, Cockayne (twice), Grisson, Hammond, Lereboullet (thrice), Pouyanne, Reuben (twice), Richter, Sauer (twice), Stenström (twice), Suner, Svensgaard (thrice), Thompson, Tribble, Uhr (four times); in three siblings by Bratusch-Marrain, Gorter, Halbertsma, Henschel, Kehl and Thomann, McGregor, Péhu, Schippers and van der Molen, Svensgaard; and in four siblings by Finkelstein, Ashby and Southam, Thomson, Carstens.

Fabricius reported the case of a family in which three children born of a mother and her first husband, and a fourth child born of the same mother and her second husband were affected. In Caulfield's case father, daughter, and son evidenced the disease. The occurrence in father, son and possibly grandson was mentioned by Schreiber; in father and son by Svensgaard and Schmid; in father, son, and father's brother by Pouyanne; in father and two sons by Lereboullet; in mother and son by Ashton; and in uncle and nephew by Schmid.

Halbertsma gives the distribution of five instances of the disease in the families of two brothers. The pedigree published by Brendle is of the greatest interest; he discovered nine cases in four families interrelated in such a manner that one case each occurred in the four sons of three sisters whose five brothers had been suffering from the disease.

For an accurate statistical evaluation of the frequency of familial occurrence one should possess the knowledge of the total number of observations of the disease among which the examples of consanguinity were detected, or, conversely, the presence or absence of familial tendency in the highest possible proportion of the observed and reported instances of the disease. Only the latter information is available, and that but on a small scale. Monrad noted 7 instances of familial occurrence in 174 cases; Uhr, 4 in 47 cases; Rinvik, 10 in 107 cases; Still, 4 in 248; Thompson and Gaisford, 2 in 209; Strauss, 2 in 221; and Lereboullet, 3 in 47 cases. Even if the statistical significance of these sporadic and incomplete data cannot be expressed numerically, they appear to make the assumption a reasonable one that, as judged by the frequency of familial incidence, a genetic factor probably plays a role in the etiology of infantile pyloric stenosis.

A further valuable criterion of the presence of hereditary influences is the incidence of the disease in twins. Numerous such observations have been recorded. Simultaneous presence of the disease in each of a pair of monozygotic (identical) twins was described by Bilderback, Card, Davis, Ford and co-workers (twice), Gelder, Halbertsma, DeLange, Lantz, Moore, Redgate, Redlin, Sheldon, Sommer, Varden. Similar occurrence in fraternal twins was noted by Monrad (twice) and Wallgren (twice). One of a pair of paternal twins showed the disease in the cases reported by Halbertsma, Knauer, McKechnie, Schmid, Thomson, Wallgren (two cases). In the case of uniovular twins, as a rule both are affected; in binovular pairs one of the pair is usually free from the disease. Although Lasch and Lereboullet reported one pair of monozygotic twins, each, with one of the pair unaffected, there is serious doubt of the monovular character of these instances. The largest collection of cases of twinning is that of Sheldon who was able to investigate the records of thirty-six sets of twins.

Concerning the frequency of twinning among infants with pyloric stenosis, Ford and his associates observed 11 pairs of twins among 436 such patients (1:36.3); Rinvik, 2 among 137 (1:68.5); Pouyanne, 1 among 35 cases (1:35); Monrad, 3 among 223 cases (1:76.5); and, finally, in 1000 collected cases Sheldon found the ratio of twinning to be 1:43.4 (the normal ratio being 1:80). The total number of cases analyzed is again too small to make statistical conclusions certain. It seems logical, however, to subscribe to Sheldon's opinion that the evidence of twinning incidence is a strong proof that pyloric stenosis of the infant has a genetic basis. It must be added that from the information now available the exact mode of inheritance of the hereditary factor cannot be stated. It does not appear to be entirely sex-linked, however, and it is apparently complemented by an environmental factor (Cockayne and Sheldon).

Closely allied to the problem of hereditary factors is the much debated question of the presence of a constitutional anlage. Attempts

have been made to ascertain constitutional patterns in the parents as well as in the infants, or to be more precise, since such investigations of infants are difficult, in children with past history of pyloric stenosis. The results have been highly contradictory. Reiche, Behrmann, Block, and others believe they have demonstrated definite constitutional stigmas in the parental group in the form of "gastropathic tendencies." Cohen and Breitbart found in 44 per cent of 27 cases allergic heredity or allergic symptoms. v. Mettenheim considers the majority of these infants to belong to a "neuropathic-asthenic" constitutional type; he also finds them often to evidence certain uniform physical traits, such as hirsutism and prominent eyes. Others (Lehmann and Bau) deny the significance or even presence of demonstrable constitutional factors.

The *intrauterine development* of the infants with pyloric stenosis shows no significant deviation from normal. Prematurity has been found with the usual frequency (Rinvik 5.8 per cent and Strauss 1.5 per cent) and the course of pregnancies has revealed nothing unusual (Strauss and Rinvik). Abnormal deliveries occur as often as generally expected (Nissen and Boecker, Strauss).

It has been long known that infantile pyloric stenosis *occurs predominantly in the first-born infant*. While the variation in the percentages of incidence reported is great (46 to 80 per cent; Barrington-Ward, Bodart and Mathieu, Faxen, McLeod, Rinvik, Robertson, Still), the average lies between 50 and 60 per cent. The frequency of first births in the general population is below or just around 40 per cent of all recorded births (Ford and associates, Salmi, Wallace and Wevill). A convenient way of comparing the available figures is to divide all births into two groups: first births and births of an order higher than first. Thus we obtain the following figures: Wallace and Wevill: first births among patients with infantile pyloric stenosis 55.6 per cent, in the general population 20 per cent; the values given by Salmi and by Robertson are as follows: 58.6 per cent and 42.5 per cent, and 51.8 per cent and 41.2 per cent, respectively. Thus the conclusion seems sound that the absolute preponderance of first-born infants among those suffering from pyloric stenosis is real. After a closely reasoned statistical analysis Ford and co-workers reached the same conclusion. Thus far, however, no plausible ideas have been advanced for the explanation of this phenomenon.

Another generally recognized finding is the overwhelming *predominance of males* among these patients. The proportions given range from 72.9 to 100 per cent (Bodley, Brown, Donovan, Fredet, Kehl and Thomann, Ladd, Lanman and Mahoney, McGahee, McLeod, Meredith, Mouriquand and Weill, Munting, Oehsenius, Oehler, Paas, Pouyanne, Raisch, Rinvik, Robertson, Schönbauer, Still, Strachauer, Strauss, Talerma, Vanden Berg, Wiedhopf and Bruhl) with the average between 85 and 90 per cent. It will be noted presently that this fact has been incorporated into the framework of some of the theories of pathogenesis



(Stolte and Ernberg). Some authors claim, but without adequate statistical evidence, that when it occurs in the female the disease has a tendency to be particularly severe.

The racial distribution of the disease has been very little studied. Lanman and Mahoney found no evidence of influence of racial factors in their cases. Direct facts to the contrary are hard to find indeed. It is very evident, however, to anyone studying the literature of the disease, that case reports from certain countries are very scarce. For instance, from Italy only 45 cases were recorded in the literature until 1935 (Colarizi). With the exception of France (Morlet, Mutel and Rémy, etc.), the same trend is found in all the other so-called Latin countries (Arquellada, Giustinian and Antonelli, Zuviria). It is, of course, true that many factors other than lack of racial affinity may lead to a meager number of cases observed and reported in any one country, but this disparity is so marked that the conclusion is almost inescapable that the Anglo-Saxon races for some reason are much more susceptible to the disease. Moreover, very few cases have been observed in Negroes (Davison) (Donovan, about 2 per cent of all cases in New York; McGahee, 2.1 per cent in St. Louis). Heile encountered a high incidence among Jews. It has also been stated that some *geographic influence* may have a role: the Alpine regions of Europe appear to be entirely free from the disease (Ramstedt).

Bayer was the first to suggest a *seasonal variation* in the incidence of the disease. He found that a considerably larger number of cases was treated during the spring quarter of the year. This variation in frequency has been attributed to changes in the diet (vitamins), enhanced endocrine activity, or hypersensitivity of the vegetative nervous system, all incidental to the changes of season (v. Mettenheim). Schönbauer and McGahee recorded similar observations, but Faxen, Wiedhopf and Bruhl, Svensgaard and others could not corroborate this assertion. The weight of evidence is certainly in favor of the absence of seasonal influence on the occurrence of the disease.

Some authors (Stolte) attempt to attach great significance to the marked *preponderance of babies who have been breast fed*. The frequency of breast feeding indeed varies from 65 to 75 per cent, but upon closer scrutiny one sees that this is about the number of infants that are breast fed normally in the age group in which pyloric stenosis is prone to appear (Behrmann, Faxen, Monrad, Salmi).

Upon analyzing our own material for the presence or absence of the factors just discussed, we find that no familial tendency can be discerned. The proportion of males is 85.3 per cent. All but three of the patients belonged to the Anglo-Saxon race, there having been in addition a Hungarian, a Polander, and a Russian. Fifty-eight per cent of the infants studied were first born and 75.8 per cent of them were breast fed. In all these latter respects, therefore, our material repeated the trend generally observed. There was a slightly higher percentage of abnormal births (one face presentation, one vertex presentation, one foot-

ling breech, one delayed second stage, and one low cervical cesarean section—altogether 16 per cent) than usually found, but no prematurity was noted. As to the influence of season, our material shows how fallacious the apparent result of the study of a short series of observations may be: Fully 50 per cent of our cases had their onset in the months of July, August, and September, a wholly unique phenomenon and obviously without significance.

#### THEORIES OF PATHOGENESIS

Before a sufficiently large number of post-mortem examinations were done the theory was advanced that the obstruction of the pyloric outlet was caused by congenital anomalies: misplaced embryonic tissue rests, such as atypical pancreatic or duodenal glandular tissue (Torkel, Ribbert cit. by Schmid, and Lehmann). With the gradual accumulation of pathologic data and with the clarification of the typical picture of the anatomic alterations it became evident that these abnormalities, together with the embryonic adenomyoma of the pylorus occasionally encountered (Magnus-Alsleben), are but rare malformations that may cause symptoms resembling true pyloric stenosis but have no significance in its etiology.

The presence of congenital anomalies near the pyloric region and elsewhere in the body but concurrent with pyloric stenosis (palatoschisis, atresia ani, congenital heart disease, agenesis of fingers or teeth, and others; Lehmann) had, however, a decided influence on the theories that conceived the pyloric lesion as a *congenital malformation*. (We now know that the total number of these birth abnormalities is too small to have any statistical significance.) The appearance of the symptoms at an early date after birth or, in some cases, at birth, and the observation of the disease in premature infants also seemed to support a congenital etiologic mechanism. Thus Hirschsprung, Finkelstein, and Ibrahim established the theory that the pyloric tumor represented an arrested stage or a complete absence of the process of involution of the fetal pylorus; the abnormal musculature thus remaining, will, "on account of spastic phenomena," lead to the clinical manifestations of the disease during the first few weeks of life. The proponents of the theory explained the frequent spontaneous improvement of cases by stating that the hypertrophied gastric musculature may, in time, overcome the obstructive resistance of the pyloric region; they further theorize for cases that develop the symptoms weeks or even months after birth by saying that these have an incomplete degree of obstruction at birth and that the phenomena of irritation, that completes the obstruction, will occur later. The only concrete evidence in support of this theory is Holt's observation that in infants with functioning gastroenterostomy the pyloric tumor persists for years. This statement has not, however, been corroborated and later observations on cases after the Fredet-Ramstedt operation reveal complete disappearance of the tumor (Lan-

man and Mahoney and Donovan). The most damaging evidence against the theory is the fact that a typical pyloric tumor has never been found in a premature infant unless it had lived for some length of time (Lehmann and Schmid). On the grounds of the accepted teratologic principles one may also object that malformations always represent a defective rather than an overdeveloped genetic process.

Another group of authors consider the pyloric tumor to be *the result of work hypertrophy* occurring in fetal life. Dietrich and also Willi (cited by Uhr) believe that obstruction of the pylorus may be due to a shortened hepatoduodenal ligament. Others see the cause of impeded pyloric function in fetal peritonitis (Heusch, cited by Schmid); periduodenitis (Ramstedt); or anatomic abnormalities such as misplacement of the cecum or superior mesenteric artery (Schmid). The supposition of all these authors is that a functional hypertrophy takes place before birth owing to mechanical obstruction of the pyloric outlet. Thomson's assumption differs only in that he postulates a "nervous incoordination" of the pyloric and gastric musculature leading to disturbance of emptying.

The so-called *spasm theory* (Wernstedt, Bromann, and Pfaundler) regards the spasm of the pyloric musculature as the primary factor and the hypertrophy as a result of the spasm. (Pfaundler originally went so far as to deny the existence of hypertrophy, accounting for the gross appearance of the pyloric region by a "shift of muscle volume and the state of spastic contracture.") Various factors have been sought to be made responsible for the initiation of the spasm: local erosion (Ernberg), irritating foodstuff, defective development of the vegetative nervous system, birth injury of the vasomotor and vomiting centers. The chief refutation of the theory has come exactly from the futility of the attempts to demonstrate these alleged initiating factors. Clinicinal investigation also failed to yield convincing evidence of neurologic disturbance of the infants affected. Moreover, the holders of this view fail to distinguish adequately between the pyloric canal and the pyloric sphincter proper, two anatomic structures of well-defined and different functions. In general, they consider the entire pyloric region as one anatomic unit. But a spasm of this region should obviously lead primarily to a hypertrophy of the wall of the body of the stomach rather than of the pyloric canal.

Because of the deficiencies of these theories, numerous ideas have been advanced to bolster or replace them.

Vollmer believes that the *alkalosis* produced by any kind of severe vomiting will bring about vagotonia and this, in turn, spasm of the pylorus.

Pirie developed the rather complex train of thought that the *hyperadrenalinemia* often noted in pregnant women causes a depression of the function of the pancreas of the fetus; this in turn leads to a hypermotility of the duodenum that interferes with the orderly opening of the

pylorus and gives rise to pylorospasm. Although Pritchard and Hillier, and Gray and Reynolds also attempted to support the role of hyperadrenalemia in the causation of the disease, the available evidence is not at all convincing.

Forssell has advanced the idea of "*disturbed autoplasmicity of the pyloric mucosa*." According to him the pyloric mucosa possesses the ability of self-regulatory movement (autoplasmicity) and may act as an important agent of the closure of the pyloric opening (so-called *torus pyloricus functionalis* or "functional pyloric stopper"). The first step in the genetic events of pyloric stenosis is, states Forssell, the impairment of this autoplasmicity. He conducted some very painstaking and ingenious radiographic investigations in proof of his ideas, but his work has remained unconfirmed.

Moore and his co-workers have shown that rats fed on a diet deficient in the *vitamin B complex* develop, particularly in the second generation, among other changes, a type of hypertrophic pyloric stenosis together with myelin degeneration of the vagus. By analogy they claim that the cause of infantile pyloric stenosis of the human being is the same. There have not been sufficient clinical investigations carried out to prove or disprove this statement by dietary studies, although the theory may have some merits (e.g., it suggests an explanation for the so-called racial affinity and familial incidence of the condition).

An ingenious theory has been published by Stolte. He came upon the idea that the hypertrophic pyloric musculature in the male infant is the counterpart of the hypertrophic uterus of the newborn female (which, as is well known, is as large as that of a 7-year-old girl), both being affected by the *growth-promoting hormone* circulating in the maternal blood during pregnancy and present in the maternal milk. The idea has obvious attractions: it checks with the sexual distribution of the disease and with the seeming frequency of breast feeding among the patients. It is hard to explain, however, why the pylorus should be particularly susceptible to the hormone; the prostate would be a more logical site. In addition to several other objections, one may mention that the measurements of the pyloric musculature show no appreciable differences in the normal male and female infants (Beumer and Hückel). However, the idea has never been subjected to laboratory research.

Lehmann considers the initial stages of hypertrophic pyloric stenosis *analogous with the essential features of cardiospasm*, the cause of which is the achalasia of the cardiac sphincter. According to the best current opinion, the pyloric sphincter (as distinguished from the musculature of the rest of the pyloric canal, a primarily propelling muscular mechanism) is in a state of tone when not actively working: this is the position in which it closes the pyloric outlet; its working condition comes about when it opens (Vertue, Kestner, and Rhumann). Thus the cause of hypertrophic pyloric stenosis is a congenital, hereditary inability of the pyloric sphincter to open, i.e., to perform its func-

tion. The consequence of this is a work hypertrophy of the pyloric musculature, upon which the task of overcoming the resistance of the sphincter falls. If this compensatory hypertrophy is of sufficient degree, no clinical symptoms will appear. Further, Lehmann postulates the presence of an additional, central factor. As a result of the persistent overload on the gastric musculature, a summation of stimuli takes place in the higher nervous centers and eventually the threshold of sensory stimuli will be reduced for the central and peripheral vagal mechanism. Finally, the threshold may be lowered to the point where minimal peripheral excitation will result in contraction of the gastric wall, hyperperistalsis, and vomiting. The clinical picture will thus consist of the manifestations of the sum of these two effects: first, the inability of the stomach to empty itself when the hypertrophy of the pyloric musculature no longer keeps pace with the work demanded to overcome the obstruction, and, second, the state of central vagal hyperexcitability. According to Lehmann, most forms of medical therapy attack the central factor, i.e., attempt to increase the sensory threshold by central depression. Conversely, the surgeon directs his effort to the breaking of the first link of the chain of events, by sectioning the sphincter and thus relieving the obstruction.

As all the theories opposed to the concept of congenital etiology, Lehmann's view is subject to the criticism that the short interval between birth and the appearance of the disease is an insufficient length of time for the development of a high degree of muscular hypertrophy. This objection is, however, a decidedly speculative one. Lehmann's hypothesis, on the other hand, has much supporting evidence in fact.

Recently Herbst (and others, cited by v. Mettenheim) demonstrated changes of degeneration in the axis cylinders and ganglion cells of the wall of the pyloric canal and stomach proper. Since in achalasia of the cardia (Hurst, cited by Vertue) similar pathologic changes have been reported, this observation would seem to make the analogy between achalasia of the cardia and achalasia of the pyloric sphincter, as postulated by Lehmann, even stronger. It could be further presumed that the nerve changes represent a failure of normal development, perhaps on a hereditary basis, which may, under favorable circumstances, correct itself by the third month of life, when, in fact, the symptoms of this disease usually disappear spontaneously.

The roentgenologic studies of Meuwissen and Slooff, Runström, Wallgren, Frimann-Dahl, Jochims, Andresen, and others have demonstrated that one can, with great precision, delineate a period of growth in the evolution of the pyloric changes. There have been very early cases observed with definite x-ray changes but without clinical symptoms (Wallgren). In instances of reoperation, a progress in the growth of the tumor has been repeatedly noted. Roentgenologically it has also been shown that the progress in the size of the tumor takes place as the result of the incorporation of new hypertrophied muscle fibers orally;

concomittantly the lumen becomes narrower and, as demonstrated by operative observations, the wall of the pyloric canal becomes increasingly thicker. Eventually a length of 10 to 24 mm. will be reached as compared to the normal length of 1 to 4 mm. These phenomena evidently fit into Lehmann's theory well. According to him the changes in the pyloric canal are those of work hypertrophy, thus a varying length of time will be required for their full development. Moreover, as long as the compensatory hypertrophy is adequate to its task, no symptoms will develop; thus, the asymptomatic cases with x-ray evidence of pyloric changes will be explained.

In a very comprehensive review of the problem Schmid has also formed the opinion that the pyloric swelling is the result of a true hypertrophy of the muscular wall, brought about by a persistent "state of tension" of both the longitudinal and the circular muscle fibers. Instead of a primary obstruction at the pyloric opening, such as the achalasia postulated by Lehmann, he suggests the presence of a somewhat mysterious "stimulus" that initiates the condition of increased tension in the muscular elements. He believes that he has found proof to identify this initiating factor with *hereditary allergy*. (In this connection it may be noted that Balyeat and Pounders, Cohen and Breitbart, and Rowe have also called attention to the possible role of allergy in the etiology of infantile pyloric stenosis.)

Of particular interest is Schmid's explanation of the strikingly uniform anatomic configuration of the pyloric tumor. Although puzzling even at first sight, the strict limitation of the muscular hypertrophy to the boundaries of the pyloric canal had not been quite satisfactorily clarified before. From considerations too lengthy to be repeated Schmid concludes that the upper limit of the extent of the tumor is determined by the anatomic disposition of the hypertrophic muscle fibers that causes them to lose their mechanical efficiency above the angle of the pyloric antrum. (It is generally agreed that the sphincter is spared of the process of hypertrophy because it is a structure apart from the pyloric canal.)

*Summary of the Theories and Facts of Etiology.*—There is no valid evidence to sustain the view that the pyloric tumor of infantile pyloric stenosis is a malformation or, in other words, a birth anomaly. Its pathologic features, its symptomatology and its response to treatment prove this lesion to be a form of quasi-physiologic tissue reaction, most likely a type of work hypertrophy, in response to some abnormal stimulus. Two fundamental questions remain to be answered. First, does the development of the pyloric tumor always occur postnatally? The best answer to this question is a qualified "yes"; while in the great majority of cases the lesion evidently develops after birth, in a few cases one must assume that at least the earlier phases of the pyloric swelling must have had their origin in utero, i.e., during the last days of intrauterine life. It must be added that this possibility does not

necessarily refute the supposition that the pyloric changes are those of a type of work hypertrophy rather than of malformation. The other problem concerns the nature of the stimulus that calls forth the series of events leading to the pyloric tumor. The identity of this stimulus is not definitely known, although a number of factors, such as factors of race and sex, the high incidence in the first born, and a strong hereditary factor, have been recognized that must have some hitherto unexplained relationship to it.

The theory that binds the known facts and assumed possibilities into the most plausible sequence of events is that of Lehmann. For the time being this must be considered the most logical hypothesis of etiology even though it, too, overlooks the effects of some important factors of pathogenesis (race and sex incidence, frequency in the first born) and leaves unsatisfactorily explained some commonly seen phenomena (early postnatal appearance of pyloric tumor). The steps in the structural evolution of the pyloric tumor have been best elucidated by Schmid.

#### SYMPTOMATOLOGY

*Incidence.*—No reliable data of incidence are found in the literature. According to Hertz (cited by McGill) 2.7 per cent of all infants below 1 year of age show the disease, but this seems altogether too high a figure. At the Henry Ford Hospital about 3 to 4 of every 1000 infants less than 1 year old have had the disease. Since about 1925, a marked increase in the number of reported cases has been noted, unquestionably due to the more frequent clinical recognition of the disease.

*Vomiting.*—At birth the child tends to be particularly lusty and well developed. The average birth weight has been recorded in the various series as about 3500 Gm. for boys and about 3000 Gm. for girls (Faxen, Mouriquand, Rinvik, Svensgaard, Strauss, Wallace and Wevill). The first days of life are also, as a rule, normal. During the third or fourth weeks of life, however, the infant begins to vomit its feedings. The vomiting first follows the intake of food by some minutes, and there may even be some meals retained. Gradually it becomes more severe and it soon reaches a point where it starts with the first gulps of food. According to the reports in the literature the most common time of the onset of vomiting is between the second and sixth weeks of life, with the peak during the third and fourth weeks (Behrmann, McGahee, Monrad, Rinvik, Salmi, Still, Strauss, Svensgaard, and Wolff) during which nearly one-half of all cases occur. Seventy to eighty per cent of the cases will appear during the first six weeks of life. The average age at the onset varies between 21 (Brown) and 28.5 days (Rinvik). The first symptoms have been observed to show in some cases as late as four, six, or even nine months, but such cases are very rare. In fact, for all practical intents the statement appears to be true that after the second, at most the third, month of life the disease is not seen (Ramstedt and v. Mettenheim). About 10 per cent of the cases start at birth.

In our material, 80 per cent made their appearance during the first four weeks of life (exclusive of three cases on which we have incomplete information).

An important characteristic of the vomitus is its freedom from bile or other duodenal contents. As a rule it does not contain blood. Only Svensgaard and Rosenbaum report important incidences of bloody vomitus (36.7 per cent and 23 per cent respectively). Ernberg finds it frequently, but gives no figure. Frank hematemesis has never been observed (Rinvik). In our series blood was noted in the vomitus once; in three instances the necessary information was not given.

In other respects an analysis of the returned stomach content yields nothing characteristic. The acidity is usually increased owing to the presence of decomposition products. In advanced cases hypochlorhydria and hypoacidity are found.

The vomiting often starts as a simple regurgitation but practically always becomes forceful and projectile in type. Projectile vomiting must be considered as the *sine qua non* of the diagnosis of infantile pyloric stenosis. It has been found present in virtually every case; even when not decidedly forceful, the vomiting is of such severity that it is only a matter of personal estimate whether one labels it projectile or merely "vomiting." Among all our cases the type of vomiting was thought to be projectile except in one instance, but in this it was extremely persistent and associated with visible peristaltic waves. (In one instance the type of vomiting was not stated.) It is characteristic of the vomiting that it is entirely refractory to the usual therapeutic measures of modification in the feeding formula, and that it is unaccompanied by manifestations of a febrile disease.

It should be noted briefly that vomiting may be entirely absent in spite of the presence of the typical pathologic changes in the pylorus (Bexelius, Findlay, Wallgren, and others). This phenomenon will be easily understood in light of the modern concept of pathogenesis of the disease (*vide supra*), and, for obvious reasons, has no bearing on the practical diagnostic importance of the symptom of vomiting.

Usually after an attempted feeding, but often independently of it, *waves of gastric contraction* can be seen passing across the child's upper abdomen from left to right. This sign, too, has been observed in almost every case reported and is the second cardinal point of diagnosis. But it is not pathognomonic; peristaltic waves of the same description have been noted in a variety of conditions other than pyloric stenosis (Gardère and Viallier, Mouriquand and Weill, Holt, Still). In our own material this sign was observed in 81 per cent of the cases.

In a number of cases the *pyloric tumor* can be palpated, usually in the right upper quadrant, high under the costal margin. The proportion of cases in which the pyloric thickening is reported to have been palpable varies quite widely: Bodley, 5 per cent; Brown, 54 per cent, palpable varies quite widely; Lanman and Mahoney, 98 per cent; Lereboullet, Donovan, 100 per cent; McLeod, 84 per cent; Meredith, 87 per cent; Still, 100 per cent; McLeod, 84 per cent; Meredith, 87 per cent; Still, 100 per



cent; Strauss, 25 per cent; Wallace and Wevill, 24.1 per cent; Wyatt, 33.3 per cent; Svensgaard, 87 per cent. Fredet can palpate it only "rarely" and Strachauer "very rarely." According to Ramstedt the palpation, for anatomic reasons, is possible only in very lean subjects: ordinarily the pylorus is located near the spine, behind the liver and under the cover of the antrum and stomach. Moreover, it has been claimed that the pyloric tumor changes its consistency from time to time (Ibrahim and Wernstedt); others deny the presence of this phenomenon (Heile and Ramstedt), but if it should exist, it could further increase the difficulties of palpation. There has been a great deal of discussion about the question of whether or not the palpation of the pyloric tumor is a requisite of diagnosis. Since the success in demonstrating this sign depends upon so many subjective factors one cannot insist on its presence for a positive diagnosis. When it is present, however, its significance is virtually pathognomonic. In the literature, instances in which a pyloric tumor was with certainty felt before, and found absent during, operation are quite rare (Downes and Ramstedt). It is, furthermore, evident that with increased experience and with a great deal of patience, the successes in palpating the tumor can be raised to about 80 or 90 per cent. Since a positive assurance that the tumor is present makes further investigations dispensable, one should attempt to demonstrate it, by all means. The diagnosis, however, can be ascertained by other methods, should one be unable to do so. We have been able to demonstrate the thickening of the pylorus in 56.0 per cent of the cases.

On account of the persistent vomiting, after a varying length of time, profound *metabolic changes* appear in the infant's organism. The most conspicuous of these is the *reduction of the volume of feces and urine*, frequently noted by the parents themselves. The scantiness of feces, which are greasy and consist mainly of bile, pancreatic juice, mucus and epithelium, is, of course, due to the lack of food entering the intestinal tract and is commonly taken for constipation, a symptom reported by the mother in about 90 per cent of the cases. In a small proportion of cases (Uhr) a spurious, "hunger" diarrhea may develop caused either by profuse intestinal mucosal secretions or by the mother's attempts to overcome the apparent constipation. The oliguria is merely another expression of the dehydration which is manifest in the entire appearance of the baby.

The most important metabolic changes take place in the *blood chemistry*. The extensive studies of Schnohr, Seckel, Maizels, and others have demonstrated that the continuance of the vomiting as the disease progresses leads to a severe chloropenia (serum NaCl 350 mg. per cent or less, Seckel) and that this, in turn, gives rise to alkalosis, azotemia, and hyposmosis. The hypochloremia may be of such degree that it brings about chloride depletion of the tissues (Schnohr). A state of disturbed consciousness will eventually ensue, the so-called pyloric coma, characterized—in addition to a mental stupor—by shallow breathing,

muscular hypertonia, and nontetanic convulsions. Findlay has expressed the view that the fall of chlorides in the urine cannot be strictly correlated with the severity and duration of vomiting and that, in some way, perhaps by the action of a toxin, the chlorides become fixed in the tissues. No corroboration of this contention has come forth from other quarters. On the contrary, it is generally held that the blood chemical changes can be taken as an index of the severity of the disease and thus they are of great prognostic value. They would deserve more practical clinical application than hitherto allotted.

In addition to hypochloruria albuminuria, acetonuria and glycosuria have at times been noted (v. Mettenheim).

In our material, unfortunately, the blood chemical studies have been so sporadic as to preclude any conclusions. The common laboratory methods (urinalysis and blood counts) routinely used on our service yielded no distinctive diagnostic information.

The final important consequence of vomiting, and usually the first one to cause sufficient alarm to suggest the necessity of a medical consultation, is the cessation of the normal gain in weight and, eventually, a *loss of weight*. Since one seldom has an accurate idea of the rate of gain of the infant prior to the onset of the disease, it is customary to compare the weight at admission to the birth weight in order to make an estimation of the magnitude of loss. This varies widely, but in a large proportion of the cases the admission weight will have fallen under the birth weight; e.g., this was the finding in 57 per cent of Tallerman's patients. Strauss records the average loss from birth weight as 240 to 450 Gm., while Svensgaard's figures are 100 to 280 Gm. The general impression is that the weight losses observed in more recent times are less than those of former years, although accurate comparable figures are not available. Among our patients the average birth weight was 3535 Gm., the average admission weight 3597 Gm.

In advanced instances of undernutrition the dehydrated, wasted infant, with its collapsed lower abdomen and prominent, tense epigastrium, makes a striking and sad picture. In patients in poor general condition the temperature is usually subnormal. At times, however, temperature elevation may be present, generally ascribed to the disturbance of the temperature-regulating cerebral center (v. Mettenheim).

*Differential Diagnosis.*—It is usually a simple matter to eliminate the possibility of infectious vomiting on grounds of the absence of high fever, dyspeptic stools, and an acute infectious disease. In the presence of the typical findings just discussed (persistent, projectile vomiting, epigastric peristaltic waves, loss of weight, and palpable pyloric tumor, to which may be added the typical blood chemical changes and the presence of constipation), there are few organic diseases of the abdomen that may lead to confusion in diagnosis (Hipsley). The rare congenital anomalies of the pylorus and peripyloric region (*vide supra*) will, as a rule, be mistaken for true hypertrophic stenosis, but such mistakes

will result in no harm if surgical treatment is resorted to as indicated by the standard operative criteria. The same is true of the obstructive lesions of the duodenum (Ladd and Burt and Tyson). Moreover, these duodenal diseases frequently may be differentiated by the presence of bile in the vomitus, and almost invariably by means of radiographic studies. Yet there will be cases where only surgical exploration will yield the diagnosis (Burt and Tyson).

It is not these lesions that create the commonest diagnostic problem but the symptom complex called pylorospasm. By definition, pylorospasm is a form of pyloric obstruction due to a purely neurogenic dysfunction (presumably spasm) of the pyloric musculature. The diagnostic criteria of this condition have not been very clearly stated but they appear to be (Shanley): a transitory character of the obstruction, a less violent, less persistent and usually nonprojectile character of the vomiting, less preponderance of involvement in the male, later onset and, in general, a less malignant course.

About the relationship of this syndrome to organic pyloric stenosis the opinions are either sharply divided or noncommittally vague, Holt claims that this condition exists only as a transitory state, wholly incapable of giving rise to a disease picture of importance. According to his view the vast majority of the instances labelled pylorospasm are mild forms of organic pyloric stenosis. Mitchell supports this view, and Ramstedt and Halbertsma admit that true pylorospasm is very rare. On the other hand Higgins, Tallerman, Tisdall and others agree that a sharp distinction should be made between the two conditions. In general the French, British, and a part of the American authors incline to a differentiation of the two disease pictures, whereas in the German literature the distinction is much less marked.

From this controversy one gains the impression that the disagreement springs from an exaggerated and unnecessary delimitation of diagnostic criteria. But for the absence of a palpable pyloric tumor, the signs and symptoms of pylorospasm reveal no essential qualitative difference from those of organic pyloric stenosis; the distinction is merely one of degree. It has been already shown, however, that the presence of the pyloric tumor is often difficult to establish and that, therefore, it cannot be considered an indispensable diagnostic sign. The hitherto puzzling phenomenon of the absence at operation of a pyloric tumor in spite of the presence of all the other cardinal signs and symptoms of pyloric stenosis—a phenomenon considered the strongest evidence in favor of the separate existence of pylorospasm—can be explained logically in terms of the modern concept of pathogenesis of pyloric stenosis; one no doubt deals, in these cases, with early examples of the disease, when the process of hypertrophy has reached only a mild degree, or else the hypertrophic changes have already begun to regress. Thus, the conclusion is inescapable that if one views the diagnostic criteria comprehensively, the differences between the two

conditions are so slight as to make the segregation of pylorospasm as a disease *sui generis* unwarranted. On the contrary, it seems likely that this symptom complex is merely a milder, more benign form of the organic stenosis. In fact, progression of this form into a more severe form with all the characteristics of organic pyloric stenosis has been observed (Uhr). Further, it seems probable that there are cases of transient vomiting caused by temporary pylorospasm, in the meaning of Holt, but by no means deserving classification as a disease entity. The differentiation between pylorospasm and pyloric stenosis is, therefore, unnecessary from the pathologic point of view; it may, however, be well to remember the distinction between the two types of disease state from the therapeutic point of view since the benign form will do well on medical management (*vide infra*).

*Roentgenologic Characteristics.*—The roentgenologist's main diagnostic problem has been the differentiation between pyloric stenosis and pylorospasm, or more precisely, the decision as to whether the case in question was a surgical or a medical responsibility. The conventional radiographic criteria (Lereboullet, Mouriquand, Viethen, Contamin) have for some time been the dilatation and general atony of the stomach with intermittent hyperperistalsis and a great delay in emptying. In contrast, in pylorospasm the stomach is found to be normal in size, hypertonic, and of more nearly normal emptying time or with an all-or-none evacuation. Obviously, these differences are to be regarded as the different phases of the same process. As the modern etiologic concept sees it, the first group of changes represents a viscus that has undergone a series of compensatory changes and is now failing in function; it is an advanced phase of the process. The other series of appearances are characteristic of the stomach in the early phase; there is evidence of obstruction but with full compensation at work. As additional evidence to the operative indications, these criteria are very helpful, as shown by Calvin and Denenholz, who, by the evidence of 60 to 100 per cent three-hour retention, were able to diagnose the presence of pyloric stenosis in every one of 96 cases. Of the 20 cases we have studied radiographically, 18 showed a three-hour retention of 75 per cent or more; in 16 cases the retention was 90 per cent or more. Of particular interest was a case in which the three-hour retention was 35 per cent, or nearly normal; this case was a typical picture of surgical pyloric stenosis and at operation displayed a well-developed pyloric tumor. It is to be noted further that in three instances, normal, and in one instance, increased, tonicity was found, and that three stomachs showed no increase in size. Nevertheless, all these viscera presented characteristic surgical findings.

Similar failures of the conventional radiographic signs, though relatively few, have been observed by others (Shanley). Andresen, Frimann-Dahl, Jochims, Meuwissen and Slooff, Runström, and others have

demonstrated that the emptying time is of secondary importance. Their findings may be summarized as follows:

Under the fluoroscope no peristalsis can be seen in the region of the pyloric canal. The stomach shadow comes to a sudden end at the pylorus. At times a widening of the prepyloric segment to the right and downward is evident, so that the greater curvature descends to the antrum abruptly and vertically. In regular intervals, deep peristaltic waves are noted as if caused by the sudden relaxation of the gastric musculature. The contrast medium must be gently pressed into the pyloric region; then it is possible to demonstrate the stringlike, narrow, and elongated pyloric canal. Roentgenograms should be taken in an oblique diameter with the patient prone. The unfailingly typical roentgen evidence of the disease is afforded by the appearance of the pyloric canal which is four to five times its normal length and only a millimeter or two in width.

Whereas few critical voices have been raised against the accuracy of roentgen diagnosis (Findlay and Shanley), the opinions concerning the advisability of the practical application of radiographic methods are sharply divided. Heile, Lereboullet, Mouriquand and Weill, Rinvik, Rohmer, and Strauss use roentgenologic examinations almost routinely and find them very useful or even indispensable. But Brown, Donovan, Ladd, Robertson, and Wyatt consider these examinations superfluous and even harmful. The usefulness of the method undoubtedly depends on many local factors. Where surgical treatment is routine, for instance, the x-ray investigation will be unnecessary for completing the operative indications; one will operate in any case. On the other hand, if one tries to select the operative cases with the greatest care, and with the help of all available means of information, the radiogram will be of decided assistance. The alleged harm that may come from the ingestion of the barium meal is probably imaginary; it has never been actually observed. We have found the roentgenologic studies helpful in nearly every case, indispensable in a few, deleterious in none.

#### TREATMENT

*Medical.*—The earliest modes of treatment of infantile pyloric stenosis were of course medical: frequent small feedings, modification of milk mixtures and milk substitutes, and lavage of the stomach in order to get rid of the decomposing foodstuff stagnant in the stomach. At times the early dietary measures appear astounding, even if not lacking in ingenuity. Fabricius Hildanus, for instance, ordered "meat-juice with olive oil" in place of the habitual "corn-pap." (It was a wise change, though, for this the first known victim of infantile pyloric stenosis made a nice recovery.)

No fundamentally new therapeutic idea appeared until the latter part of the nineteenth century when Heubner introduced the use of hypnotics on the theory that the alleged cause, the spasm, would thereby

by relieved; *tinctura opii* and various papaverine compounds became the most popular of these.

Apparently it was Strümpel who, in 1904, first tried out and advocated atropine (in the form of tincture of belladonna) for the relief of the spasm that was the generally accepted etiologic factor. This drug made slow headway in popularity and became widely used only after the 1920's.

In 1914, Birk described the beneficial effect of corn-meal mush as a substitute for liquids in the infant's diet. Independently, Sauer, in this country, called attention to the usefulness of farina paste, at about the same time. The rationale behind these attempts to feed food of thick consistency was that thus a stimulus is supplied for the deficient peristolic function (gripping force) of the stomach (Rogatz). "Thick feeding" with the administration of atropine and juggling of the feeding schedule and milk modifications has become the standard conservative means of treatment in this country. The same plan with different substances is used elsewhere in the world. Gastric lavage is still practiced by some but, in view of the better understanding of the blood chemical changes, it is discouraged, since it tends to aggravate chloride depletion.

The most important innovation in the drug therapy of the disease in almost forty years was the application to internal treatment of the drug eumydrine by Drucker and Usener of Copenhagen (1926). This methylnitrate derivative of atropine was originally proposed for use as a mydriatic (hence its name), but later it was found that it had the full internal action of atropine with only one-fiftieth of its toxicity. With its use remarkable results have been obtained.

Here the pharmacologic properties of atropine (and eumydrine) and its possible mode of action in infantile pyloric stenosis may be briefly considered (McSwiney and Vertue). The pyloric sphincter is normally closed. When a wave of contraction starts in the pyloric antrum the sphincter relaxes and remains open for five to six seconds. About a second before the wave reaches its summit the sphincter closes again and stays closed during the remainder of this wave and afterwards until the next. These movements are governed by the intrinsic nervous system. The opening and closing can be influenced by local events (acidity and osmotic pressure of the gastric contents, and intraduodenal pressure). The stomach has a double nerve supply: sympathetic and vagal; the mechanism thereby governed is rather complex. Section of the vagi causes diminished tone, slow peristalsis, and delayed emptying. Stimulation of the vagi usually causes dilatation of the pyloric sphincter and increase in the tone and movement of the stomach; but if the stomach is already in a state of high tonus, the effect is the opposite. Stimulation of the splanchnics causes the body to relax and the sphincter usually to contract; but if the sphincter is already hypertonic, it relaxes. The net result depends not only upon which nerve is stimulated but also upon the condition of the stomach at the moment. Atropine has

a general paralytic effect on nerve endings in the stomach. Given intravenously to cats, it causes a general relaxation of the stomach, a fall in intragastric pressure, and an arrest of movements. If one now presumes that the primary difficulty in infantile pyloric stenosis is the spasm of the sphincter, then medicinal doses of atropine (or eumydrine) must be blocking impulses to the sphincter without inhibiting peristalsis—a highly complex and difficult goal to attain. But if it be supposed to be an achalasia, the explanation is much simpler; the general relaxation in which the sphincter shares is reached before peristalsis is abolished.

It may be added that the central depressant action of atropine may be of more therapeutic importance than is generally appreciated (Lehmann).

There have been a number of other drugs employed in the treatment of infantile pyloric stenosis but none achieved any popularity: subcutaneous suprarenin, scopolamine, and hyosine mixtures (so-called *vasano*), papaverine (Bókay) in combination with eumydrine, and a whole series of hypnotics. The application of the latter group was by some developed into the so-called twilight-sleep therapy, during which the child may be kept unconscious for a number of days or even weeks. The central idea in the rationale of the use of cerebral depressants is the recognition of the fact that these infants present a high degree of nervous excitability, as propounded in Lehmann's theory of pathogenesis. The presence of gastric hyperperistalsis caused by many superficial stimuli other than ingestion of food is one of the manifestations of this state. Moreover, the extent and intensity of vomiting of these children are not direct functions of the degree of pyloric obstruction; as Ramstedt has pointed out, in obstructing pyloric ulcer of the adult even the highest grade of obstruction will fail to lead to a picture similar to the protracted vomiting and excessive gastromotor irritability that are commonly observed in the stenotic infant. (See also Haverschmidt and Bókay.)

As curiosities one may mention the methods of treatment with x-ray irradiation (Wiener), diathermy (Tobler) and foreign-protein injections (v. Mettenheim).

In the early 1920's, Gerstley called attention to the period of relative cessation of irritability immediately after a spell of vomiting. He advocated, therefore, refeeding of small amounts of food ten to fifteen minutes following the last attack. The method appeared to have merits in selected instances.

Particular stress should be laid on the importance of subcutaneous and intravenous fluid therapy (including blood transfusions), which became widely used only in the early 1920's, and, together with the improved hygienic conditions of the infants' ward and the refinement of infant nursing care, has been the all-important factor in the production of the low mortality rates of the latter years.

*Surgical.—History:* The development of the surgical treatment of infantile pyloric stenosis lagged a few paces behind the general advance of surgery, perhaps because it required an extra measure of fortitude to put the knife to the feeble infant body. And since, as the most obvious line of attack, the early operators attempted to apply to the problems of the infant technical procedures devised for adults, the decision of making the trial had to wait until the value of the method had been established and the difficulties of technique overcome. Even thereafter the progress was slow. The story of the surgical therapy of infantile pyloric stenosis is a fitting illustration of the old truth that discoveries are seldom achieved by bold leaps but rather by short and faltering steps that as often slide back as stride forward but always tread the path smoother for those coming behind.

The first operation ever performed for the disease certainly cannot be regarded a step forward. Cordua of Hamburg, Germany, in 1892, performed a jejunostomy on a male infant sick with pyloric stenosis. The outcome was fatal. This type of operation was never again recorded in the literature.

The next operative intervention, and at the same time the first one in the United States, was that of Willy Meyer who, in 1897, performed a posterior gastroenterostomy with Murphy button.\* A few weeks later Stern of Germany did an anterior gastroenterostomy. Both these cases ended fatally shortly after the operation.

The credit for the first successful operation of any type must go to Löbker, a German, who in 1898 obtained complete cure with a posterior gastroenterostomy. During the subsequent fifteen years gastroenterostomy, anterior in more severe cases, posterior if the patient's condition permitted it, became the most popular procedure.† From 1897 till 1908, it was performed fifty-two times with a mortality of 59.6 per cent (Abel, Dufour and Frédet).

In the latter part of the nineteenth century the so-called "pyloric divulsion" of Loretta was a commonly employed operation for various types of pyloric stenosis in the adult. The main steps in its technique were the opening of the stomach and the introduction of a mechanical dilator with which, then, the constricted pyloric canal was forcibly enlarged. With the advent of pyloroplasty the procedure fell into disrepute, but Nicoll of Glasgow applied it with some success to the treatment of infantile pyloric stenosis. Altogether, thirty-six such interventions were reported by him and others until 1908, with an over-all mortality of 41.1 per cent. Nicoll later added a gastroenterostomy to

\*Gastroenterostomy was first attempted by Welsler in 1881; this was an anterior operation; the first posterior gastrointestinal anastomosis was performed by v. Hacker in 1889.

†It is of more than passing interest to record that among the fairly large number of gastroenterostomies performed in infants only one reported case of marginal ulcer has been found; this ulcer occurred in a 9-month-old baby and was fatal (Kausch).



the divulsion, and his mortality with this combined operation (seven cases) was around 30.0 per cent. In 1906, he published the description of a so-called V-Y pyloroplasty in conjunction with the divulsion; he lost only one of the six cases in which he used this technique. It is worthy of note that in his report he, rather vaguely, mentions that under some circumstances (he failed to mention under what circumstances) the pyloroplasty must be made without opening the mucosa.

Nicoll's creditable results were not duplicated by others using the same method. The combined mortality rate in 113 cases in which all the methods so far mentioned were employed (reported up to 1908) was 50.5 per cent. It was generally recognized that a good share of the responsibility for the high mortality had to be ascribed to the technical difficulties of the procedures. To simplify the intervention, Braun, in 1900, introduced the use of the then rather new Heineke-Mikulicz pyloroplasty (first performed in 1887) for infantile pyloric stenosis. The technique attained some measure of popularity and its results were slightly better than those of the older methods.

As used in the infant, however, pyloroplasty had decided disadvantages. While generally recognized, these objectionable qualities were first critically analyzed by Frédet. He wrote (in 1908): "*Cette manière de faire n'est pas, il faut l'avouer, sans inconvénients. Elle oblige à ouvrir une cavité septique, à sectionner la muqueuse qui saigne. Il est malaisé d'assurer l'hémostase en faisant la suture de la muqueuse, difficile également d'obtenir une suture parfaitement étanche.*" Frédet undertook to eliminate the first two technical imperfections of the procedure (the opening of an infected cavity and the sectioning of the vascular mucosa with its danger of hemorrhage) by carrying his longitudinal incision only as far as the submucosa, leaving the stomach unopened. He then proceeded to suture the muscularis transversely, in the standard manner. His first operation was performed on Oct. 12, 1907.

It invites speculation to note that he had in his grasp the solution of the third technical problem, the difficulty of closure of the hypertrophic muscle wall, but somehow he did not realize it. He describes in detail his inability to place accurate sutures into the muscle layers of the pylorus; the excessive tension would tear the thread out. He was even obliged to leave a diamond-shaped area of submucosa uncovered by muscle. Although in this case recovery was satisfactory, the idea of overcoming the difficulties of cross-suturing, required in the Heineke-Mikulicz pyloroplasty, by omitting the sutures was apparently too revolutionary to enter his mind.

Frédet's experiment was exactly duplicated by W. Weber in Germany. Weber, who was unaware of the work of Frédet, nevertheless evolved the same technique, and on Dec. 3, 1908, performed it with success. Of his next two cases thus treated, however, one died of hemorrhage.

This and Kausch's severe criticism of the procedure, which followed Weber's publication by a few days, were important factors in dampening the interest in the new operation. Kausch, then one of the high priests of German surgery, condemned the method in strong words, claiming that the cross suturing, far from increasing the lumen of the pylorus, will aggravate the obstruction by folding the mucosal lining into creases. At any rate, the operation was not again reported upon until 1912, when Ramstedt\* revived it with the addition of his own modification.

He first performed it in September, 1911, following Weber's technique step by step. (Frédet's previous article was unknown to him, too.) He was impressed by the ease with which the edges of the wound in the muscular wall of the pylorus gaped and the submucosa bulged. The patient continued to vomit for a few days and in general had a hard time. Then suddenly the vomiting ceased and thereafter the infant made an excellent recovery. Ramstedt remembered Kausch's warning about the cross suturing of the thick muscle layer; he also recalled that the edges of the wound could be closed only under a great deal of tension. The sudden turn in the postoperative course could be explained in but one way, he thought: the sutures gave way, the wound righted its direction, allowing the edges to separate and the mucosa to protrude, as they had a tendency to do, and thus the obstruction was overcome. In the future the operation should be carried out in this, the only physiologic way, he concluded. On Jan. 18, 1912, he had an occasion to try this idea, and the patient in this case recovered smoothly. In the same year he reported his two operative cases, setting forth very clearly the rationale of his method and advocating it as the technique best suited to deal with the problem of infantile pyloric stenosis.

There is little doubt that the popularity of the submucous operation takes its origin from Ramstedt's first publication. Even for some time after this article had appeared, Frédet's and Weber's work remained forgotten. It is only fair to remember this when one assigns credit for the invention of this operative technique. It is true that like so many other scientific discoveries, it was the product of an unwitting cooperation among at least three men,† but the greatest share of recognition still must go to Ramstedt. It is undeniable, for instance, that in his original paper Frédet is vague about the operative indications of his submucous pyloroplasty; he himself continued to use gastroenterostomy as the method of choice until 1921; for thirteen years after its first

\*In the English language medical literature there is some confusion concerning the correct spelling of this name. With the exception of his first publication, all Ramstedt's papers contain his name spelled with one "m." The "Minerva" (Jahrbuch der gelehrten Welt) (1930) also gives it with a single "m."

†If one keeps looking, one finds earlier and earlier seeds of the later thought. According to Kausch, in Mikulicz's Clinic a submucous pyloroplasty was in use years before Frédet had any conception of it. (It was so bad they never published it, he says.) Nicoll appears to have employed some sort of submucous operation, although his statement with regard to this is vague. And finally, Weber seems to have got his inspiration from Rietschel.

description he did not use the submucous pyloroplasty at all! In fact, it appears well established that Frédet took up the operation again on the spur of the growing popularity of Ramstedt's procedure, as if re-learning it from the German. And Weber's work, as already mentioned, remained in complete obscurity.

Some importance is lent to all this argument about priority of credit by the question of the designation of the operation. Ramstedt advocates the use of the term pyloromyotomy, an excellent suggestion. But in general it is the name of "Ramstedt's operation" that has become accepted, save in France where Frédet gets all the credit and Ramstedt is unknown. If one holds to the questionable habit of eponyms, Frédet-Ramstedt or Frédet-Weber-Ramstedt would seem to be the fair designation to use.

In the United States the beginning of surgical therapy of infantile pyloric stenosis was marked by the unsuccessful attempt of Willy Meyer, already quoted. To Elting belongs the credit for the first surgical cure of the disease in this country (1904). In the subsequent years the excellent work of Scudder, Richter, and Downes made gastroenterostomy the most commonly used procedure. These three surgeons had a combined mortality rate of slightly over 20 per cent (Downes), a very good record at the time. The introduction of the Frédet-Ramstedt technique by Downes (April, 1914)—first in conjunction with pyloric divulsion, then in the classical form—marked the advent of a new era, in which American surgeons (particularly Donovan, Ladd, and Strauss) attained unsurpassed results.

*Surgical Versus Medical Treatment.*—Before the introduction of the Frédet-Ramstedt operation the surgical therapy of infantile pyloric stenosis was an *ultima ratio physicorum*, much as primary surgical intervention for bleeding peptic ulcer is today (Bauer). If everything else failed the surgeon was given a last chance to save the infant. Gradually the situation changed, and at present the topic of discussion concerns mainly the limits of the right of the surgeon to intervene. Both for this reason and because an occasional voice is still raised in condemnation of surgical treatment it seems desirable to review the respective merits of the surgical and medical methods of therapy.

In such evaluations in the past, mortality statistics have frequently been resorted to. Raw mortality statistics should be treated with great precaution in any case, and particular care is necessary in the case of infantile pyloric stenosis. There are inherent and almost inevitable factors in the medical and surgical series that tend to color the conclusions seriously. In clinics using both medical and surgical therapy (and these are in an overwhelming majority), the more severe cases will naturally fall to the lot of the surgeon. Thus the surgeon's mortality rate will have a heavy initial handicap. This factor of difference is only partly eliminated by the comparison of statistics from institutions using either exclusively medical or exclusively surgical

TABLE I

## MORTALITY IN SURGICALLY TREATED CASES (FRÉDET-WEBER-RAMSTEDT OPERATION)

AUTHOR'S NAME	COUNTRY	YR. OF PUBLICATION	NO. OF CASES	NO. OF DEATHS	MORTALITY (%)
Still	England	1923	29	11	37.9
Bolling <sup>1, 5</sup>	U. S. A.	1925	454	68	15.0
Strachauer <sup>1, 5</sup>	U. S. A.	1927	48	1	2.1
Barrinton-Ward	England	1928	79	2	2.5
Clopton <sup>2, 5</sup>	U. S. A.	1928	81	10	12.4
Heile	Germany	1930	100	3	3.0
Kohl	Germany	1931	63	5	7.6
McLeod	England	1931	13	3	23.0
Page <sup>1, 6</sup>	England	1931	150	15	10.0
Schönbauer	Austria	1931	17	1	5.8
Hakki-Leriche	France	1932	20	3	15.0
Paas	Germany	1932	41	2	5.0
Lanman <sup>1, 5</sup>	U. S. A.	1933	425	27	6.3
Munting	Germany	1933	58	7	12.0
Nissen	Germany	1933	50	4	8.0
Wiedhopf	Germany	1933	15	2	12.5
Oehler <sup>2, 5</sup>	Germany	1934	42	6	14.0
Ramstedt <sup>1</sup>	Germany	1934	65	2	3.0
Spamer <sup>4, 6</sup>	Germany	1934	27	0	0.0
Wallace <sup>2, 5</sup>	Scotland	1934	145	36	24.8
Decker	Switzerland	1935	10	0	0.0
Kehl <sup>3, 6</sup>	Germany	1935	51	2	3.9
Rohmer	France	1935	34	4	11.4
Thompson <sup>1, 5</sup>	England	1935	209	30	14.4
Vanden Berg <sup>2</sup>	U. S. A.	1935	34	1	2.9
Bodley <sup>2, 5</sup>	U. S. A.	1936	60	1	1.6
Meador <sup>2</sup>	U. S. A.	1936	45	10	22.0
v. Haberer <sup>1, 3</sup>	Germany	1937	112	8	7.1
Frédet	France	1937	54	2	3.7
Kirschner <sup>2, 6</sup>	Germany	1937	89	5	5.6
McGahee	U. S. A.	1937	114	13	11.4
Raisch <sup>2, 5</sup>	Germany	1937	33	1	3.0
Salmi	Finland	1937	26	8	29.9
Strauss <sup>1, 9</sup>	U. S. A.	1937	431	9	2.0
Wamsteker	Germany	1937	36	0	0.0
Brown <sup>1</sup>	U. S. A.	1938	41	0	0.0
Lereboullet <sup>1</sup>	France	1938	49	1	2.0
Mouriquand	France	1938	32	3	9.4
Pouyanne <sup>2, 7</sup>	France	1938	35	1	2.9
Tallerman	England	1938	98	14	14.3
Bodart <sup>6</sup>	France	1939	34	3	8.5
Wyatt	U. S. A.	1939	100	3	3.0
Dijkhuizen	Germany	1939	130	7	5.4
Donovan <sup>1, 5, 8</sup>	U. S. A.	1940	410	1	0.3
Griep	Netherlands	1940	28	1	3.4
Ladd <sup>1, 5</sup>	U. S. A.	1940	340	9	2.7
*Meredith <sup>1, 5</sup>	U. S. A.	1940	137	9	6.5
Rinvik	Norway	1940	65	4	7.6
Robertson <sup>1, 5, 7</sup>	Canada	1940	402	52	12.9
Shanley <sup>1</sup>	Ireland	1940	22	3	13.6
Williams	England	1941	70	10	14.0
Levit <sup>6</sup>	England	1941	146	5	3.4
Total			5,399	428	7.9

\*Incision: Right rectus with transverse opening of posterior rectus sheath.

<sup>1</sup>Anesthesia, ether.

<sup>2</sup>Anesthesia, local.

<sup>3</sup>Anesthesia, chloroform.

<sup>4</sup>Anesthesia, none.

<sup>5</sup>Incision, right rectus.

<sup>6</sup>Midline.

<sup>7</sup>Right subcostal

<sup>8</sup>110 consecutive cases without death.

<sup>9</sup>167 consecutive cases without death.

methods, since the number of cases obtainable from such sources is quite small.

This leads to the next source of error: the set of diagnostic criteria employed. Whether or not one uses the term pylorospasm, one has ample evidence that there are mild forms of pyloric obstruction that do well on any careful conservative management. These cases, as mentioned, seldom figure in surgical statistics. The diagnostic criteria of many medical reports, on the other hand, are so loose that it seems to be a certainty that a considerable proportion of the reported cases treated conservatively do not represent, for practical purposes, the same disease that most of the surgeons are called upon to treat.\* For instance, Ernberg, Monrad, and Svensgaard do not consider the presence of a palpable pyloric tumor or the x-ray appearance of the stomach at all important in making their diagnosis. Moreover, medical authors frequently exclude from their computations cases that they arbitrarily consider "hopeless" or dead of "causes other than pyloric stenosis." The surgeon has to include among his failures every case that fails to leave the hospital cured, although a considerable proportion of his fatalities are nonsurgical (see Table VI). There have even been medical statistics computed on the end results after subtraction of those cases that had to be operated upon because of failure of the medical treatment.

With all these restricting factors in mind, what can one learn from the statistics of mortality?

In Table I there are listed the end results as to survival of patients treated with the Frédet-Weber-Ramstedt operation, or one of its modifications, published in the more important reports since 1920. Cases described before 1920 were not incorporated in this compilation since either they were negligible in number or they have been included in later reports. Similar criteria were used in choosing the medically treated cases for Table II.

It is evident that both excellent and poor results have been obtained with either method of therapy, the mortality rates varying within fairly wide margins not only from country to country and from period to period but also from author to author in the same time period and geographic unit. Some sporadic statistics on conservative treatment (mainly from the Scandinavian countries) exceed all but the best American surgical results. The average mortality rates of the total number of cases studied in either group leave little to choose between the two methods. The fact, however, that all the factors of error tend to work in the disfavor of the surgical statistics make it strongly probable that surgical management is superior to the medical mode of treatment as judged by the mortality rate alone.

\*This statement must be particularly true of the patients in Vertue's cases that were treated in the outpatient clinic.

TABLE II  
MORTALITY IN CONSERVATIVELY TREATED CASES

AUTHOR'S NAME	COUNTRY	YR. OF PUBLICATION	NO. OF CASES	NO. OF DEATHS	MORTALITY (%)
Haas	U. S. A.	1922	40	0	0.0
Ibrahim	Germany	1923	400	41	10.2
Meagher	England	1926	22	3	13.5
Schelble	Germany	1926	29	0	0.0
Monrad	Denmark	1938	223	10	4.5
Bischoff	Germany	1929	46	5	10.8
Kemkes	Germany	1929	31	6	19.0
Wolff	Germany	1930	92	10	2.2
Paas	Germany	1932	25	1	4.0
Lindquist	Sweden	1932	43	8	18.6
Behrmann	Germany	1933	25	4	16.0
Faxen	Sweden	1933	126	8	5.5
Munting	Germany	1933	66	11	16.6
Willi	Germany	1933	87	5	5.7
Eckardt	Germany	1934	46	3	6.5
Eckstein	Germany	1934	92	17	18.4
Svensgaard <sup>2</sup>	Denmark	1935	119	9	5.0
Vonderweidt	France	1935	28	5	17.9
Braithwaite <sup>1</sup>	England	1938	21	3	14.3
Dobbs <sup>1</sup>	England	1939	20	3	15.2
Vertue <sup>1</sup>	England	1939	21	0	0.0
Rinvik <sup>2</sup>	Norway	1940	72	2	2.9
Total			1,734	154	8.8

<sup>1</sup>Treated with eumydrine alone.<sup>2</sup>Treated in part with eumydrine.

TABLE III  
LENGTH OF HOSPITALIZATION

AUTHOR'S NAME	SURGICAL (IN DAYS)	MEDICAL (IN DAYS)
Munting	36	76
Paas	42	77
Eckstein	34	91
Eckardt	45	70
Birk	38	78
Rinvik	27	62
Svensgaard*	--	94
Wamsteker	40	79
Average	37.4	78.4

\*Medical treatment alone.

TABLE IV  
COMPARATIVE MORTALITY RATES  
IN PRIVATE AND HOSPITAL CASES

AUTHOR'S NAME	PRIVATE CASES		HOSPITAL CASES	
	NUMBER OF CASES	MORTALITY (PER CENT)	NUMBER OF CASES	MORTALITY (PER CENT)
Bolling	40	2.5	239	15.0
Still	128	10.9	98	56.1
Thompson	31	3.2	178	16.4
Thomson	11	18.2	28	73.0
	210	7.1	543	26.0

This fact, however, could not alone assure priority for the surgical method. If, for instance, Svensgaard's results (in spite of all the possible sources of error therein contained) could be reproduced on a wide scale, his method of treatment would be preferable, provided it equaled the surgical type of management in other respects as well. For it is still a sound principle that, given equal prospects of success, the conservative management of a disease is the one of preference. Such medical results, however, require the utmost in expert nursing, in equipment, and medical attention. It appears an unquestionable fact that a true mortality rate of 5 per cent or less with purely medical measures is a harder task to achieve than a similar surgical mortality rate. Surgical management places a lesser strain on the resources of the average hospital than does medical therapy. Thus a socioeconomic factor enters the discussion and it favors the surgical type of therapy. This therapy has the further important advantage of offering a shorter period of hospitalization (Table III), which on the average is less than one-half that required by the medical method. (In our own series the average hospital stay was 14.8 days, with only one over thirty and five over twenty.) Not only does this mean less cost but also less opportunity for intercurrent infection. (The importance of this factor is well illustrated by Table IV.)

The only sound conclusion from all these considerations is that, as usual, the best road lies in the middle. As formerly emphasized in this study, one must recognize the two main types of the disease: the mild one, eminently suited to conservative management, and the severe one that may, at the expense of much money, time, and patience, be carried through the critical first twelve weeks of life but would be cured by operation quickly and with at least no greater danger to life than the medical management entails. Shanley adds to these two a third group: one that is manageable either medically or surgically. The problem is, then, to make a wise selection and apply the suitable treatment.

In any event, however, it is important to keep in mind that if surgery is to give its best result, the infant should not be carried along stubbornly on a medical regime until its general condition so deteriorates as to make the operative risk prohibitive. Earlier operations have contributed to the prodigious improvement of operative results nearly as much as better preoperative preparation, the two being, in a sense, inseparable (see Table V).

*Operative Indications.*—The logical way of attacking the problem of selection is to make a trial with conservative management and if this fails within a determined period of time proceed with the surgical intervention. Kirschner, v. Haberer, Heile, and Ramstedt institute medical treatment for three to four days and if this does not produce a definite improvement, recommend operation. Schmid operates if the child is in such poor condition that it cannot withstand a period of

TABLE V  
DECLINE OF MORTALITY FROM YEAR TO YEAR

AUTHOR'S NAME	PERIOD OF OBSERVATION	NUMBER OF CASES	MORTALITY (PER CENT)
Bolling	1915-1920	175	17.1
	1923-1925	130	8.5
Lanman*	1915-1923	125	10.4
	1923-1928	150	7.0
	1928-1931	150	2.0
Ladd*	1932-1935	162	4.9
	1936-1939	177	0.56
Robertson	1914-1923	81	24.4
	1924-1933	212	13.0
	1934-1939	109	3.6

\*Reports from the same institution (Children's Hospital, Boston).

trial; if the three- to four-day period of medical regime is unsuccessful; or if, in spite of symptomatic improvement, after several days it is still impossible to introduce a sufficient amount of food to assure the resumption of weight gain. Lehmann starts with conservative measures in every case but advises operation if the loss of weight continues after six to eight days. Downes' period of trial is ten days, provided the initial weight loss is less than 20 per cent of the body weight; in the latter case, operation is the method of choice. In seeming contrast Lanman and Mahoney, Donovan, Strauss, and Robertson believe in operation for every case in which the diagnosis of hypertrophic pyloric stenosis has been made. Upon further consideration, this is not as radical as it appears. These men prepare their patients very adequately, therefore they employ two to three days for conservative measures and since the large majority of the patients on conservative trial (at least 80 per cent, Munting) will be found to require operative treatment, only 20 per cent or less of all the patients operated upon by the "all-out surgeons" would theoretically be amenable to a reasonably short medical regime. At any rate, these surgeons have the strong argument in their favor that the number of cases they take out of the pediatrician's hands is small and they are the best risk of all.

Our routine has been similar to that of the more conservative surgeons. After a period of five to six days of the usual medical treatment (hydrating measures, "thick feeding," modified milk formulae, atropine,\* and, if necessary, blood transfusion) the patient is operated upon unless a definite improvement of the symptoms has taken place, preferably with some weight gain. According to individual cases this period of trial may vary but it has only twice been longer than ten days, with an average of 4.7 days.

*Operative Contraindications.*—Before the general acceptance of the surgeon's intervention as a legitimate mode of treatment, the most com-

\*We have had no experience with eumydrine.



monly encountered contraindication to operation was the moribund condition of the patient. At the present it is rare to see this picture. One should not operate, also, in the presence of a severe infection, but occasionally exceptions must be made. In infants whose disease began at two months, and particularly three months, of age, conservative treatment is practically always successful; it may be said, therefore, that surgical intervention in most of these cases is unnecessary (Donovan and Shanley).

*Preoperative Prognosis.*—The all-important prognostic criterion before operation is, of course, the general condition of the infant including its state of nutrition, hydration, and general strength. It follows that the duration of symptoms before operation bears a direct relationship to the mortality rate. Thus, Goldbloom and Spence have found that the mortality of those infants that had had the disease for less than four weeks was only one-third that of the infants suffering from the disease for more than four weeks. Lanman and Mahoney, Tallerman, and McGahee arrived at exactly the same conclusion. The loss of weight at the time of operation is only another way of expressing the same fact; the majority of observers, accordingly, find that the magnitude of weight loss is in linear relationship to the rate of mortality (Goldbloom and Spence: if weight of infant is below 7 pounds, the mortality expectancy is three times higher than in infants weighing more than 7 pounds) (Tallerman, Wallace and Wevill). In general breast-fed infants are in a better position to withstand the operation (Tallerman). Goldbloom's and Spence's conclusions from the analysis of thirty-two postoperative fatalities was that an infant who has been breast fed, who has been ill for less than four weeks, and whose loss of weight is less than 20 per cent of its best previous weight has a mortality expectancy of zero. (It may be mentioned that formerly much was said about Quest's number; this was taken to be one-third of the birth weight of the infant, the loss of which was thought to foretell a sure fatality. It has been shown to be an unreliable criterion.)

It has also been said that the prognosis is poorer the earlier after birth the first symptoms appear (v. Mettenheim, Reiche, Feer, and Langstein). According to Heubner, infants whose disease shows a familial tendency do poorly.

The number of our postoperative deaths is so small that our corresponding data cannot be correlated with the above findings.

*Preoperative Preparation.*—The above conclusions sufficiently emphasize the obvious importance of restoration of the normal nutritional state of the body to as complete a degree as possible. The results of blood chemical investigations have clearly shown that the chief factors in the metabolic disturbance of the infant are the dehydration and chloride loss. Both can be readily corrected by saline or glucose-saline

infusions.\* How profoundly these simple measures have affected the success of surgical treatment is shown by the fact that without exception the great reduction of the mortality rates followed directly after the introduction and popularization of parenteral fluid therapy in the early 1920's (Table V). It can be said without danger of exaggeration that this was as important a factor as the increase in surgical skill.

Prior to operation, preferably on the morning of operation, the stomach should be lavaged. Repeated lavages, however, are to be discouraged. Some prefer to leave a stomach tube in place (Donovan and Spamer), but we find this unnecessary as a routine measure.

*Operative Technique.*—In general, preoperative medication is seldom used (Bodley and Meader). Shanley recommends seconal, Ramstedt luminal. We find no advantage in using it. The choice of anesthesia has been a somewhat debated point. Opinions are almost equally divided between open ether inhalation (Bolling, Donovan, Ladd, Meredith, Page, Raisch, Ramstedt, Robertson, Strachauer, Thompson and Gaisford, and v. Haberer) and  $\frac{1}{2}$  or  $\frac{1}{4}$  per cent novocain local infiltration (Bodley, Kirschner, Meader, Oehler, Pouyanne, Shanley, Vanden Berg, Wallace and Wevill); a few use ethyl chloride (Robertson) or chloroform (v. Haberer, Kehl and Thomann); Spamer operates without anesthesia. The disadvantages of local infiltration are, in our opinion, somewhat more pronounced, namely, the danger of evisceration during operation, the possibility of novocain intoxication (Brown), reduced postoperative wound healing, and increased technical difficulty because of the restlessness of the patient. It is only very seldom that, in our days, one has to operate on a child so debilitated that drop ether inhalation will endanger its life. Brown has pointed out the very considerable danger of novocain intoxication by a simple arithmetic example. The introduction of 20.0 c.c. of  $\frac{1}{2}$  per cent novocain into a 5-pound infant is proportionate to the injection into an adult of 150 pounds of 600.0 c.c. of the solution. Our experience has been rather mixed, having used novocain local infiltration twenty-one times and open ether thirteen. During our last eight operations ether was the anesthetic agent.

There have been three main types of incision used in the cases reported: high right rectus (Bodley, Bolling, Clopton and Hartmann, Donovan, Lanman and Mahoney, Oehler, Raisch, Strachauer, Thompson and Gaisford, Wallace and Wevill), high midline (Bodart and Mathieu, Kehl and Thomann, Kirschner, Page, and Spamer) and right subcostal (Pouyanne and Robertson). Meredith uses a right rectus incision but splits the posterior rectus sheath transversely. In our series, fourteen incisions were right rectus muscle-splitting and twenty were high, short midline. The latter type of incision is our personal preference. The most important feature of the incision, however, is

\*As a simple illustration of the efficacy of this preparation it may be mentioned that, in spite of the varying but generally persistent vomiting, our patients reached the end of the preoperative period with a net gain of weight (average admission weight 3597 Gm.; average weight at operation 3,711 Gm.).

that it be high and short. A long incision only causes needless evisceration, trauma, and shock without any gain in the facility of operative technique.

The technique of the pyloromyotomy has been, in the overwhelming majority, the Frédet-Ramstedt procedure. The simple steps of this operation have already been outlined. A few additional facts may be here recorded, after the work of Browne on the anatomy of the hypertrophic pylorus. One important feature of the vascular supply of the pylorus is that the superficial arterial branches fail to anastomose at the mid-point from their origin, thus the well-known "bloodless line" is formed. It is important to remember that two deeper vascular branches are almost invariably seen during operation: one, with its accompanying vein is found running across the duodenal end of the incision, just at the important fornix of the mucosa, to which it forms a very useful indication. The other deep vessel appears in the inner layers of the musculature towards the other end of the wound and occasionally causes trouble from bleeding. The generally emphasized rule to remember about the Frédet-Ramstedt operation is that it should be ample in length; the right end of the incision should start about 1 or 2 mm. short of the visible junction between the whitish, opaque, and solid pylorus and the bluish translucent and flaccid duodenum; it should extend well into the pyloric antrum, curving upwards in its left third to follow the bloodless line between the superficial blood vessels. A mere exposure of the mucosa is not enough. At least one-half inch of it should be exposed in the middle of the incision and as much as possible near each end. This is easy except over the zone of adhesions (as mentioned previously) where serosa, muscle, and mucosa split together or not at all. The landmark of the vessel described and the recognition of the annular constriction over the zone of adhesion will prevent injury to the duodenal mucosa here.

In dissecting through the thick muscular wall various maneuvers have been used. V. Haberer and Kirschner cut with one sharp sweep of the knife until mucosa is met. (To facilitate vision, Kirschner used a specially constructed loupe.) Bolling, Downes, Heile, and others deepen the cut about halfway through the muscle layer and thereafter continue with blunt dissection. Lanman and Mahoney, Donovan, and Raisch make the incision just deep enough to penetrate the peritoneal covering and complete the dissection with a blunt instrument, such as a pair of mosquito forceps. Fuchs uses small hooks to pry the edges apart after a shallow sharp incision. Robertson separates the lips of the wound with dissecting scissors.

Among the modifications of the Frédet-Ramstedt technique the Strauss pyloroplasty appears to have been the most successful, at least in the hands of its inventor. Strauss dissects more widely around the mucosa and prepares muscle flaps which he unites above the mucosa. He claims that his cases show much less postoperative distress, mainly vomiting.

Heile makes a counterincision into the pyloric wall, directly opposite the usual location of the incision. Mayo proposes to interrupt the vagus by excising part of the omentum in addition to the standard Ramstedt maneuver. Gohrbrandt advocates the excision of a wedge-shaped piece of the hypertrophied muscular tissue in order to prevent rapid closure that might cause recurrence. Bodley turns a peritoneal flap to cover the wound. Seeger injects saline solution into the pyloric tumor to facilitate its dissection. Ombrédanne, Raybaud (cited by Ramstedt) and Wolfson add a transverse incision to the distal end of the usual longitudinal one. In all these attempts at improvement the greatest value of the Frédet-Ramstedt procedure, its simplicity, is compromised without any increase in efficacy; the operation is merely made more cumbersome and time-consuming.\*

Knoflach has carried out extensive experiments on dogs with a view to determining the advisability of modifications in the classical technique of pyloromyotomy. He found no procedure that could equal the advantages of the standard Frédet-Ramstedt operation. He particularly emphasized, as a result of his research, the importance of the location of the incision in the true longitudinal axis of the pyloric canal. If obliquely placed, he found the incision to close over too fast to permit a release of the obstruction.

In our cases the standard Frédet-Ramstedt technique was employed with the exception of one case in which, because of complications in the technical steps, a resection of the pylorus had to be done. The infant recovered nicely. (There have been three other successful pyloric resections for infantile pyloric stenosis reported in the literature. Mátyás, Ritter, and Rupp.)

The commonest complication during the operation is the injury of the duodenal mucosa. This has been reported rather frequently in the literature (Bodart and Mathieu, twice; Bolling, five times; Kohl, six times; Lanman and Mahoney, three times; McLeod, four times; Nissen and Boecker, three times; Oehler, twice; Pouyanne, three times; Raisch, once; Robertson, "a few times"; and Strachauer, twice). The general agreement of opinion is that this mishap does not in itself jeopardize the operative result, provided it is recognized and adequately dealt with. A purse-string suture with some reinforcing Lambert stitches is usually adequate to prevent leakage; it must be remembered that the superior duodenal wall, where this accident invariably occurs, is rather flaccid and has little tendency to leak (Browne). Lamson proposes a plastic flap, prepared from the muscular lips of the wound, to cover up the defect. The best way to treat this danger of technique is, of course, prevention, the rationale of which has been pointed out repeatedly (*vide supra*). Once the pyloromyotomy is completed, it is wise to test for

\*It is noteworthy that in recent times the two obsolete surgical procedures, Loretta's pyloric division and gastroenterostomy, have been revived for use in the treatment of infantile pyloric stenosis by Foranitti and v. Mettenhelm, respectively.

an accidental opening by gently pressing the stomach and duodenal contents toward the site of incision. Serious consequences are relatively rare in the literature (Robertson, Kohl, Lanman and Mahoney reported peritonitis resulting in death), but our experience is rather unpleasant with this complication. Among our cases the duodenum was opened in six instances. Of these, one patient made an uneventful recovery; one required resection of the pylorus followed by a Billroth I type of gastroduodenostomy and developed a gastric fistula which healed in 37 days; the third one developed a moderate wound infection, leaving the hospital in 28 days; the fourth became complicated by a duodenal fistula, which eventually cleared up but required 24 days of hospitalization; the fifth one continued to vomit intermittently for about 22 days from causes that apparently had no direct relationship to the duodenal accident; in the last one, the wound healed rather slowly and convalescence was sluggish but no direct effect of the mishap could be noted. In four of these cases, drainage was instituted—the only cases in which we did this—and these four did the least well, two of them developing fistulas. Briefly then, from our experience, accidental opening of the duodenal mucosa, even if recognized and repaired immediately, forecasts the probability of a stormy postoperative course, particularly if drain is used in closure, but does not seriously influence the long-range results or mortality rate.

As a complication encountered during operation one may also mention the failure to find a pyloric tumor. The etiologic and diagnostic implications of this phenomenon have already been discussed. The absence of the pyloric tumor should not preclude the performance of the Frédet-Ramstedt operation. These cases invariably manifest severe and typical preoperative symptoms, frequently entirely refractory to medical measures. Downes (two cases), Kirschner, Lanman and Mahoney, Mouriquand and Weill (two cases), and Thompson and Gaisford found a dramatic improvement after the carrying out of the typical pyloromyotomy. Although Higgins warns against any operative procedure on the pylorus in these cases, there can be little doubt that the easiest course is to carry out the pyloromyotomy, except in cases where the diagnosis was questionable, cases that should not as a rule come to the operating table in any event. V. Mettenheim goes as far as advocating pyloromyotomy for certain cases of a pure "gastrospasm," that is persistent vomiting without organically demonstrable pyloric change. (Of course, in all such cases one must exclude the possibility of some other organic lesion by careful exploration.)

There has been slight variation in the technique of closure as reported in the literature. All authors insist on careful suturing in layers. About the only important exception to this is Lee's practice, who uses through-and-through inabsorbable sutures: he claims that his postoperative wound healing has been much improved by this method. The suture material has been catgut in all instances where mention is made of it,

with the exception of Ladd, who uses silk. Some (Clopton and Hartmann) use inabsorbable suture material for stay sutures while using catgut for the rest of the closure. We close in careful layers and have used catgut fifteen times and silk eighteen times (in one case our record does not specify the suture material); for the past three years we have employed silk alone. Our number of wound infections was too small to be correlated with the suture material used.

*Postoperative Course and Treatment.*—The majority of infants continue to vomit to a lesser or greater extent for a short period of time after operation. In general this time is found to be around two to three days (Page). Munting observed complete cessation of vomiting immediately after operation in only 28 per cent of his cases, and Eckstein in only 38 per cent of his cases. There have been various explanations proposed for this postoperative vomiting. V. Haberer, for instance, states that most of the cases manifesting this postoperative symptom show blood in their vomitus preoperatively; thus, the presence of mucosal lesions would be presupposed that require time for healing. Others claim (v. Mettenheim) that these infants are particularly excitable, i.e., in their cases the central nervous factor is particularly prominent. An explanation near at hand would be to presume that in these cases the pyloromyotomy was not complete enough. From the findings at reoperation reported by Fröhlich, Gaisford, Hess, Nobel, Noetzel, and Sauermondt, Ramstedt argues that this is not the case. His explanation of the phenomenon of temporary postoperative vomiting and of the total failure of the operation to cure will be discussed briefly later. Dietrich contends that the kinking of the duodenum brought about by the dilatation of the body of the stomach which, consequently, assumes a lower position, is responsible for the postoperative persistence of vomiting. As Ramstedt points out, this must be a rare factor. Without looking for controversial reasons, however, and simply considering that most of these infants have been vomiting for three weeks or more before operation, one would expect that a period of readjustment will be necessary after the obstruction has been overcome. The rapidity of readjustment of the disturbed emptying mechanism is, in fact, surprising in the large majority of cases.

Because of this period of readjustment it has been suggested by Faber and Davis that postoperative feeding be started twenty-four or forty-eight hours after the time of operation in order to provide a physiologic rest for the stomach. These authors claim to have shown that there is a reduction of motility of the stomach for two to five days postoperatively, demonstrable by roentgenograms and fluoroscopy. The soundness of delayed feeding, however, has been questioned by all the most experienced surgeons (Robertson). The universal custom is to resume feeding very soon after operation, the interval varying from a few minutes to four hours. Exception should be made in cases of perforation of the duodenum where the feeding schedule may preferably start twenty-four hours later than usual.

The composition of the diet fed postoperatively varies widely. Modification of cow's milk, breast milk, whey, and combinations of these are used. The important principles are the very gradual increase in amounts and the careful selection and timing of the new articles introduced.

The usual supportive measures (parenteral fluids, blood transfusion, etc.) are now universally used. It is also a universal practice to entrust the regulation of the postoperative feeding to the pediatrician.

Almost always after the surgical intervention a moderate temperature elevation is noted (Munting, Rohmer, and Strauss), which is a more accentuated counterpart of the similar finding in adults and which subsides in two to three days. It is more pronounced than in the adult probably because of the differences in the physiologic response.

In our series the vomiting ceased gradually on the second or third day in the largest number of cases (57 per cent). In one case vomiting never occurred postoperatively, and in one after the eighth postoperative hour; in five, it stopped during the first twenty-four hours; in two, within four days; in one, within five days. One patient continued to vomit for ten days, one for twenty-two days and one for twenty-three days. In twenty-three of our cases (excluding the fatal ones) there was a postoperative temperature elevation of 100° F. or more. This, however, was higher than 102° in only seven cases and only in one instance did it last more than two days. The average discharge weight was 3968 Gm., which signifies an average postoperative gain of 224 Gm.

*Postoperative Complications.—Causes of Death:* The postoperative complications directly attributable to the surgeon's intervention are peritoneal infection, wound infection and wound separation, hemorrhage from the pyloric or abdominal wound, anesthetic complications, shock and such intra-abdominal complications as adhesions or volvulus (Ramstedt). In the same group one should also include deficient postoperative results, but these will be discussed under a different heading.

In analyzing these complications, it should be borne in mind that no accurate figures are available in the literature in regard to their milder forms and that whatever figures are quoted are taken from mortality statistics.

Peritonitis is more common than the reports on the incidence of duodenal perforation would lead one to expect. Obviously, either a large proportion of the accidental injury of the duodenal mucosa is not recognized or some other, as yet unidentified, source of infection must be responsible. Peritonitis in these infants is always fatal; it forms about 10 per cent of all the postoperative fatalities.

It has been many times noted that wounds in stenotic infants, although in general not especially prone to develop severe infections, have a tendency to imperfect and delayed wound healing, with thin serous drainage and stitch abscesses (McGahee). Thus, evisceration or simple wound disruption has been reported in higher percentage of these cases than of other surgical procedures in infants (Bodley, Lanman and

Mahoney, Page, and Rohmer). The obvious reason for this behavior has been suggested to be the poor nutritional state of the infant. Ladd believes, but is unable to quote quantitative proofs, that the blood vitamin C level must be subnormal in these infants and recommends prophylactic administration of this substance. That adequate preoperative preparation of the infant has an important bearing on the occurrence of wound disruption can be gathered from its markedly lower incidence in the more recent reports. In this connection it should be mentioned that postoperative hernias are quite rare in these patients (Bolling).

Many authors (v. Haberer and Ladd) consider postoperative hemorrhage the most dreaded complication. The bleeding may take place from the pyloric incision (Bolling) or from the abdominal wound (Mouriquand and Weill, and Bolling). Painsstaking hemostasis in the wall of the pyloric canal has been insisted upon by these surgeons, although others believe that if the incision is properly placed the danger of bleeding is negligible with no hemostasis whatever (Browne and Meredith). In any event, postoperative hemorrhage is an important cause of death, being responsible for about 5 per cent of all postoperative deaths.

Anesthetic complications, postoperative pneumonia and pulmonary atelectasis, following pyloromyotomy often are not purely surgical misfortunes. As has been pointed out repeatedly, this operation is such a light procedure that it taxes the infant's physical resources only slightly (Lanman and Mahoney, Bodley, Thompson and Gaisford, Wyatt). In the large majority of cases a greater share of the responsibility must be referred to the debility of the child caused by preoperative delay or lack of preparation. These complications form the largest single source (about 10 to 15 per cent) of fatalities in the large early collections of cases.

Much the same argument holds true for postoperative shock. Its frequency as cause of death was about on par with or slightly below that of postoperative pulmonary complications.

Postoperative adhesions, volvulus, or other forms of intestinal obstruction are rare. Their incidence has not apparently changed with the changing results of operative treatment.

The not strictly surgical complications after pyloromyotomy are gastroenteritis and terminal inanition, also called decomposition or atrophy. A comparison of these postoperative mishaps with the true surgical complications yields interesting conclusions. In Table VI the largest published collection of fatalities (Ramstedt) is grouped in three classes. Group 1 contains the so-called nonsurgical causes, i.e., those that have their origin in the debilitated general condition of the infant. These infants were practically moribund when they reached the operating table. In Group 2 are comprised the causes that are partly surgical—at least insofar as pulmonary complications are concerned—



TABLE VI  
CAUSES OF DEATH IN 143 SURGICALLY TREATED CASES  
(RAMSTEDT)

GROUP	NATURE OF CAUSE OF DEATH	NUMBER OF CASES	(PER CENT)
1	Extreme physical weakness before operation, leading to decomposition, atrophy, collapse or inanition postoperatively	58	40.5
2	Intercurrent postoperative infection, viz., broncho-pneumonia, gastroenteritis, influenza	35	24.5
3	Postoperative complications proper, viz., operative shock, hemorrhage, peritonitis, wound infection	50	35.0

but also either partly or mainly, as in cases of gastroenteritis, medical. Finally, in Group 3 are arranged the purely surgical causes formerly discussed. As has already been said, the responsibility for the pulmonary complications is debatable; gastroenteritis, on the other hand, is certainly a predominantly medical problem. Among other facts, its being reported most frequently from the crowded, poorly protected English infants' wards bears this out clearly. If one now makes an approximate calculation, and such is the only calculation one can make, one finds that at least half of all the postoperative fatalities are ultimately due to medical causes. This fact throws fresh light on the debate about the respective merits of the surgical and medical types of treatment on grounds of mortality statistics (*vide supra*).

In analyzing postoperative complications and causes of death, it is well to remember that, properly speaking, the discussion should be largely in the past tense. The picture has so radically changed in the last ten years that the figures quoted above, and used because they are the only available ones, hardly apply to present conditions. The only postoperative complication that has remained relatively unaltered in its frequency is infection (peritoneal and of the wound), but even infection has lost much of its importance as a lethal factor. Because of the changed operative indications, because of the realization of the importance of preoperative preparation, and because of the improved hygiene of the infants' ward, the medical causes of postoperative complications have become markedly reduced. Besides infection, the only operative dangers of consequence the infant now faces are shock, pneumonia, and technical mistakes, a minimum of which will persist by reasons inherent in the very nature of surgery.

Among our own patients, in two instances (7 per cent) moderately severe wound infection developed but no wound disruption occurred. Mild wound infection (i.e., stitch abscess) was noted in nine instances (32 per cent). We practice careful hemostasis throughout, and perhaps for this reason have had no postoperative hemorrhages. There were two fatalities (mortality rate 5.9 per cent).\* One of these patients was

\*Recently another successful case has been added to this series, changing the operative mortality to 5.8 per cent.

operated upon in the presence of an evident severe respiratory infection and died in twenty-four hours, of bronchopneumonia. Autopsy left no doubt that the pneumonia had been present when the operation was undertaken. Operative intervention had, however, been considered the lesser of the risks. The other lethal case was one of a purely surgical death—peritonitis on the fifth postoperative day. During operation no viscus had been perforated and this fact was confirmed by the necropsy findings.

*Operative Results.*—The worth of an operation can be measured by the double standard of immediate and late results.

In judging the immediate results of the Frédet-Ramstedt operation it would be desirable to proceed on the basis of some definite criteria of success, but, unfortunately, such criteria have never been established and, indeed, are probably impossible to define. The data most generally accepted as denoting success are the cessation of weight loss and resumption of gain of weight within a reasonably short time postoperatively; conversely, when this fails to take place, the operation is a failure. Although this length of time varies widely, in some cases perhaps embracing such a long period that the point of beginning of improvement may fall outside the limits of true operative cure, one must accept the judgment of the surgeon who is called upon to decide whether a secondary operation is necessary. When the surgeon acknowledges that reoperation is indicated, he recognizes that the first operation was a failure. By this standard, then, all patients who survive without reoperation are taken to be successes. This index of operative success is broad but fairly reliable, and it is the only one available. In assessing the number of reoperations one must exclude the cases of gross and obvious technical error and the cases of mistaken diagnosis not recognized at the time of the first operation. The gross rate of reoperation will thus be about 3 per cent, with a corrected incidence of about 2 per cent (Fröhlich, Gaisford, Hess, Lanman and Mahoney, Nobel, Nötzel, Page, Ramstedt, Rinvik, Sauermondt). The rate of immediate satisfactory results of the Frédet-Ramstedt operation is, therefore, 97 to 98 per cent, less the number of operative fatalities which at the present time can be placed between 1 and 2 per cent. This is a result unexcelled by any other major operative procedure.

At this juncture the question arises, What is the cause of the failures not accounted for by gross technical error and error in diagnosis?

In the absence of definite knowledge with respect to the cause and pathogenesis of infantile pyloric stenosis, the answer must be one of speculation. Taking into consideration all the etiologic possibilities, the Frédet-Ramstedt operation may have its point of attack on any one or more of the following four anatomic planes: (1) the sphincter pylori; (2) the hypertrophic musculature of the pyloric canal; (3) the nerve pathways in the wall of the pyloric canal and perhaps also in the sphincter itself; and (4) the submucosa and mucosa (by permitting

their full unfolding). The opinion is practically unanimous that the effect on the mucosa and submucosa is of secondary importance. Likewise, there is general agreement in regard to the great importance of the completeness of the section of the hypertrophic pyloric musculature. The advice is constantly stressed that the incision should be carried high on to the gastric wall, as close to the boundary of the duodenum as practicable, and as far down as the level of the submucosa. (Unquestionably the "gross errors of technique" mentioned above result from the disregard of these cautions.) Curiously, however, many surgeons (Hess, Nobel, Nötzel, Ramstedt, and Sauermondt) have remarked that at reoperation the incision in the pyloric wall is usually found ample in terms of gross anatomy. There would, then, remain two possible explanations for the initial failure. One would be the assumption that the nervous pathways involved in the causation of the disease have not been adequately severed. It does not, indeed, seem unreasonable to postulate that the disruption of some as yet unidentified nerve fibers has some bearing on the operative result, although the exact nature and the precise extent of this relationship is not at all clear. It is less compatible with logical thinking, however, to accept the intactness of these hypothetical nerve paths as the sole and full source of the persistence of pyloric obstruction. Much more in keeping with sound reasoning is the second possible supposition, i.e., that in a certain proportion of cases the sphincter pylori is not included in the pyloric incision. This structure, it will be remembered, does not partake in the hypertrophy of the pyloric musculature; its location thus becomes rather hidden and its proper cleavage is made the more difficult owing to the dangerous "zone of adhesions" directly adjacent to it. Proceeding on the theory of Lehmann, it may be presumed that the unsectioned sphincter will continue to offer resistance to passage through the pyloric opening, although to the naked eye the separation of the hypertrophic muscle bundles appears sufficient. In discussing the problem of operative failures Ramstedt likewise considers the accidental omission of the sphincter from the incision as the important factor. However, not subscribing fully to Lehmann's theory, he assumes that this omission, which he believes to be very common, is of no consequence in the majority of cases; occasionally, though, it will lead to a persistence of the preoperative symptoms. In support of the interpretation according to Lehmann's theory one may mention further that a second operation, which invariably consists of an enlarging of the original incision and thus affords a better opportunity to sever the sphincter, as a rule results in prompt relief of the symptoms.

The role of central nervous factors in the evolution of the disease picture of infantile pyloric stenosis must be borne in mind when discussing poor operative results. In a very few cases these may presumably be so preponderant as to preclude the possibility of complete cure by mechanical means alone.

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The most common cause of death in the patient with aortic aneurysm is rupture of the aneurysm into the peritoneal cavity. The rupture may occur at any time, but is most likely to occur during the operation. The rupture may be fatal, but if caught early the patient may survive. The rupture may be fatal, but if caught early the patient may survive. The rupture may be fatal, but if caught early the patient may survive.

## 5142712

OF 24 CASES WITH TYPICAL CASES OF INFANTILE PHENOL STENOSIS SEEN IN  
THE WARDEN FORD HOSPITAL IN THE PAST YEAR.

DATE: 12-1-41		SEX DISTRIBUTION:	RACE:
1000 12-1-41	10 Males	29 (5.00%)	All white—41. Certain
1000 12-1-41	24 Females	5 (14.79%)	20-30: 1. Polish; 1. Russian; and 1. Hungarian

PREGNATAL HISTORY, BIRTH:	ORDER OF BIRTH:	FEEDING HISTORY:
All pregnancies normal, full term; all deliveries normal, except:	First born 18 (54%)	Breast 22 (73.8%)
1. Face presentation	Others 13 (42%)	Mixed 1 (2.5%)
2. Vertex presentation, low forceps	No data 3	Bottle 6 (20.7%)
3. Cervical ec-carean section for funnel pelvis		(No data, "vomiting since birth" 3)
4. Footling breech		
5. Low forceps (cause?)		

AGE AT ONSET:		MONTH OF ONSET:		DURATION OF SYMPTOMS:	
Birth	4	Jan. Feb. Mar	5 cases	Mean	18.3 days
First week	4	Apr. May June	6 cases	Longest	60.0 days
Second week	6	Jul. Aug. Sept.	17 cases	Shortest	2.0 days
Third week	6	Oct.-Nov. Dec.	6 cases		

The long-range results of pyloromyotomy can be studied in the numerous follow-up investigations made with the view of determining the presence or absence of possible etiologic factors. The conclusions of these extensive works of research are in general agreement (Mouriquand and Weill, Oehler, Rinvik, Runström, Schlesinger, Strauss, Uhr, Wamsteker, and Wyatt) that, by practically all standards of testing, these patients are, in their later life, as normal as any comparable group of persons from the general population. Certain roentgenologic signs persist to indicate the site of the former abnormality (Runström, Viethen, and Andresen), but even these tend to disappear after puberty and, in any event, have no apparent clinical significance.\*

Among our own cases, the immediate results consisted of thirty complete cures, one partial cure, and one failure (exclusive of the two fatal cases). A reoperation in the partially cured case brought about a very satisfactory permanent result. The instance of failure was probably the effect of mistaken judgment. This patient had a history of over a year of persistent vomiting, refractory to all forms of conservative management. Operation was undertaken as a long-chance attempt to help him. A reoperation elsewhere was also unsuccessful. As the child grew older it became evident that he was feeble-minded and what had been taken for persistent vomiting had in fact been rumination.†

#### SUMMARY AND CONCLUSIONS

On grounds of the pertinent literature of the past fifty years—with special attention paid to that of the past twenty years—and with the help of the clinical analysis of thirty-four cases treated in the division of general surgery of the Henry Ford Hospital, the problems of etiology, symptomatology, and diagnosis of infantile pyloric stenosis have been briefly surveyed and its surgical treatment more exhaustively discussed.

From the best evidence extant it appears that infantile pyloric stenosis is probably the result of achalasia of the sphincter pylori. The gross pathologic lesion represents a form of work hypertrophy of the musculature of the pyloric canal. Strong secondary central nervous factors play a part in the coloring of clinical manifestations. There is strong evidence that in the etiology of the disease a hereditary factor plays an important part. The preponderance of males, first-born infants, and members of the so-called Nordic races among the patients is real but its etiologic meaning is not understood.

Persistent forceful vomiting, palpable pyloric swelling, visible peristalsis of the stomach, loss of weight, hypochloremia, hypochloruria, and obstipation are the cardinal findings. Of these only the palpable pyloric tumor has pathognomonic significance, but it is frequently absent.

\*It should be added that the late results of cases managed by medical means are as good as those of the operative cases.

†As to late results, our investigation is now in progress.

## SYNOPSIS—CONT'D

POSTOPERATIVE FEVER:	CESSATION OF VOMITING:	LENGTH OF POSTOPERATIVE HOSPITALIZATION:
Exclusive of fatalities:	Exclusive of fatalities:	Mean 14.8 days
Temp. of 130° F. or more	Immediately P. O. 1	Five More than 20 days
in 23 cases	8 hr. P. O. 1	One More than 30 days
Of these, only one longer	24 hr. P. O. 5	
than 24 hr.	2 to 3 days P. O. 18	
Temp. above 102° F. in 7	4 days P. O. 2	
cases	5 or more days P. O. 5	

## OPERATIVE RESULTS:

Complete cure	30 cases*
Reoperation necessary	2 cases
One: Here with complete cure	
One: Elsewhere with poor result	
(Diagnosis probably incorrect)	
Deaths 2 cases	
1 Peritonitis fifth postoperative day	
1 Ba. pneumonia 24 hr. postoperatively	

## SUMMARY OF X RAY FINDINGS (20 CASES)

Tone:	Size:	Peristalsis:	3 hour retention:
Hypo 9	Large 7	Hypo 9	90% or more 16
Normal 3	Normal 2	Normal 3	80% 1
Hyper 1	Small 1	Hyper 4	75% 1
No data 7	No data 10	No data 3	60% 1
		Reverse 1	30% 1

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\*Recently another successful case has been added to this series.

## SYNOPSIS—CONT'D

Fourth week	5
Fifth week	2
Sixth week	3
Seventh week	0
Eighth week	1
No data	3

## ASSOCIATED DISEASES:

One indirect inguinal hernia
One thrush
One impetigo

## PROJECTILE VOMITING:

Present
Absent
No data

31
1
2

## VISIBLE GASTRIC PERISTALSIS:

Present
Absent
No data

## PALPABLE PYLORIC "TUMOR":

Present
Absent
No data

17
13
4

## BLOOD IN VOMITUS:

Present
Absent
No data

1
30
3

## LENGTH OF CONSERVATIVE PREOPERATIVE TREATMENT:

Mean	4.7 day
Only two cases over	10 days

## ANESTHESIA:

Ether	13
Local—Novocain $\frac{1}{2}\%$	21
—Novocain $\frac{1}{4}\%$	
In last 3 years: Ether alone	

## INCISION:

Right rectus	14
Epigastric midline	20
Of last 22 cases only	
5 right rectus	

## TYPE OF OPERATION:

Frédet-Weber-Ramstedt	33
Resection of pylorus, Billroth I, gastro duodenostomy	1

## WOUND CLOSURE:

- All in layers  
Four drained:
1. Duodenal perforation; duodenal fistula—60 days' hospitalization
  2. Duodenal perforation; healing satisfactory
  3. Duodenal perforation; resection of pylorus; gastric fistula—37 days' hospitalization
  4. Duodenal perforation; intermittent vomiting for 22 days; final result satisfactory

## SUTURE MATERIAL:

Catgut	15
Silk	18
No data	1
In last 3 yrs. only silk used	

## WOUND INFECTION:

Superficial	9
Deep (but without separation)	2
(Excluding cases in which drainage was used and fatal cases)	

## OPERATIVE FINDINGS:

Typical appearances of pylorus in 32 cases.

In one, no true pyloric swelling was present. Pylorus was firm and hard due to spasm. Standard Frédet Weber Ramstedt procedure brought complete cure. In another, pylorus showed very slight hypertrophy. Pyloromyotomy brought no improvement. This case was later diagnosed as rumination.

## POSTOPERATIVE COURSE OF 6 PATIENTS WITH ACCIDENTAL PERFORATION OF THE DUODENAL MUCOSA

- (1) Uneventful recovery; postoperative stay 15 days.
- (2) Excision of pylorus; Billroth I, drainage, gastric fistula; postoperative stay 37 days.
- (3) Slight wound infection, recovery otherwise smooth; postoperative stay 28 days.
- (4) Drainage, duodenal fistula; postoperative stay 21 days.
- (5) Drainage, slight serous drainage, otherwise healing satisfactory; vomiting for 22 days.
- (6) Wound healed well, no drain; vomiting subsided slowly after 23 days.



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# Book Reviews

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## Books Received

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A SHORT HISTORY OF CARDIOLOGY. By James B. Herrick, M.D., Emeritus Professor of Medicine, Rush Medical College, Chicago. Cloth. Price \$3.50. Pp. 258, with 48 illustrations. Springfield, Ill., 1942, Charles C Thomas, Publisher.

CLINICAL ANESTHESIA—A MANUAL OF CLINICAL ANESTHESIOLOGY. By John S. Lundy, M.D., Mayo Clinic. Cloth. Pp. 771, with 266 illustrations. Philadelphia and London, 1942, W. B. Saunders Company.

FIRST AID—SURGICAL AND MEDICAL. By Warren H. Cole, M.D., F.A.C.S., Professor of Surgery, University of Illinois, Chicago, and Charles B. Puestow, M.D., Ph.D., F.A.C.S., Chicago. Cloth. Pp. 351, with 92 illustrations. New York and London, 1942, D. Appleton-Century Company, Inc.

ABDOMINAL AND GENITO-URINARY INJURIES. By Military Surgical Manuals, National Research Council. Cloth. Pp. 243, with 28 illustrations. Philadelphia, 1942, W. B. Saunders Company.

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ROENTGEN TREATMENT OF DISEASES OF THE NERVOUS SYSTEM. By Cornelius G. Dyke, M.D., F.A.C.R., and Leo M. Davidoff, M.D., F.A.C.S., Columbia University-Jewish Hospital, Brooklyn. Cloth. Price \$3.25. Pp. 198, with 12 illustrations. Philadelphia, 1942, Lea and Febiger.

CHANGES IN THE KNEE JOINT AT VARIOUS AGES. By Granville A. Bennett, M.D., Hans Waine, M.D., and Walter Bauer, M.D., Harvard Medical School. Cloth. Price \$2.50. Pp. 97, with 31 illustrations. New York, 1942, Commonwealth Fund.

BLOOD SUBSTITUTES AND BLOOD TRANSFUSIONS. By Stuart Mudd, M.A., M.D., Professor of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia, and William Thalhimer, M.D., Division of Human Serum, Public Health Research Institute of New York. Cloth. Price \$5.00. Pp. 407, with 94 illustrations. Springfield, Ill., 1942, Charles C Thomas, Publisher.

THE SURGERY OF PANCREATIC TUMORS. By Alexander Brunschwig, M.D., F.A.C.S., Professor of Surgery, University of Chicago. Cloth. Pp. 421, with 123 illustrations. St. Louis, 1942, C. V. Mosby Company.

THE MAKING OF A SURGEON. By Ernest V. Smith, M.D., D.Sc., F.A.C.S. Cloth. Price \$3.00. Pp. 344, with 41 illustrations. Fond du Lac, Wisconsin, 1942, Berndt Printing Company.

SURGICAL PATHOLOGY. By William Boyd, M.D., LL.D., M.R.C.P. (Ed.), F.R.C.R. (London), Professor of Pathology, Toronto. Cloth. Pp. 813, with 504 illustrations and 16 color plates. Philadelphia, 1942, W. B. Saunders Company.

MANUAL OF DERMATOLOGY. By Donald M. Pillsbury, M.D., Marion B. Sulzberger, M.D., and Clarence S. Livingood, M.D. Cloth. Pp. 421, with 109 illustrations. Philadelphia, 1942, W. B. Saunders Company.

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LYMPH NODE METASTASES: INCIDENCE AND SURGICAL TREATMENT IN NEOPLASTIC DISEASE. By Grantley Walder Taylor, M.D., Institute of Surgery, Harvard. Cloth. Price \$8.00. Pp. 498, with 61 illustrations. New York, 1942, Oxford University Press.

THE HEMORRHAGIC DISEASES AND THE PHYSIOLOGY OF HEMOSTASIS. By Armand J. Quick, Ph.D., M.D., Associate Professor of Pharmacology, Marquette University School of Medicine, Milwaukee, Wis. Cloth. Price \$5.00. Pp. 340, with 24 illustrations. Springfield, Ill., 1942, Charles C Thomas, Publisher.

SULFANILAMIDE AND RELATED COMPOUNDS. By Wesley W. Spink, M.D., F.A.C.P. Cloth. Price \$3.00. Pp. 374. Chicago, 1942, The Year Book Publishers, Inc.

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THE BIOLOGICAL ACTION OF THE VITAMINS, A SYMPOSIUM. By E. A. Evans, Jr., University of Chicago. Cloth. Pp. 227, with 20 illustrations. Chicago, 1942, University of Chicago Press.

SURGICAL CLINICS OF NORTH AMERICA, Dec., 1942, vol. 22. By many contributors. Cloth. Pp. 300, with 66 illustrations. Philadelphia, 1942, W. B. Saunders Company.

SURGICAL CLINICS OF NORTH AMERICA, Oct., 1942, vol. 22. By many contributors. Cloth. Pp. 261, with 63 illustrations. Philadelphia, 1942, W. B. Saunders Company.

FRACTURES. By Paul B. Magnuson, M.D., F.A.C.S., Northwestern Medical School, Chicago. Cloth. Price \$5.50. Pp. 511, with 319 illustrations. Philadelphia, 1942, J. B. Lippincott Company.

ORTHOPEDIC SUBJECTS. By Military Surgical Manuals, National Research Council. Cloth. Pp. 306, with 77 illustrations. Philadelphia, 1942, W. B. Saunders Company.

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MANUAL OF OXYGEN THERAPY TECHNIQUES. By Albert H. Andrews, Jr. Cloth. Price \$1.75. Pp. 191, with 30 illustrations. Chicago, 1942, The Year Book Publishers.

ORTHOPEDIC SUBJECTS. By Military Surgical Manuals, National Research Council. Cloth. Price \$3.00. Pp. 306, with 79 illustrations. Philadelphia, 1942, W. B. Saunders Company.

TREATMENT OF FRACTURES. By Guy A. Caldwell, M.D., F.A.C.S., University of Louisiana School of Medicine. Cloth. Price \$5.00. Pp. 303, with 92 illustrations. New York, 1943, Paul B. Hoeber, Inc.

**BURNS, SHOCK, WOUND HEALING AND VASCULAR INJURIES.** By Military Surgical Manuals National Research Council. Cloth. Price \$2.50. Pp. 272, with 80 illustrations. Philadelphia, 1943, W. B. Saunders Company.

**RENAL LITHIASIS.** By Charles C. Higgins, M.D., Cleveland Clinic, Cleveland. Cloth. Price \$3.00. Pp. 140, with 18 illustrations. Springfield, Ill., 1943, Charles C. Thomas, Publisher.

**PRINCIPLES AND PRACTICES OF OBSTETRICS.** By Joseph B. DeLee, M.D., Consultant in Obstetrics, Chicago Lying-in Hospital and Dispensary, and J. B. Greenhill, M.D., Attending Obstetrician, Michael Reese Hospital, Chicago. Cloth. Price \$10.00. Pp. 1101, with 841 illustrations. Philadelphia, 1943, W. B. Saunders Company.

**ESSENTIALS OF PROCTOLOGY.** By Harry E. Bacon, M.D., F.A.C.S., F.A.P.S., Head of the Department of Proctology, Temple University. Cloth. Price \$3.50. Pp. 345, with 168 illustrations. Philadelphia, 1943, J. B. Lippincott Company.

**DISEASES OF THE NOSE, THROAT AND EAR; MEDICINE AND SURGERY.** By William L. Ballenger, M.D., F.A.C.S., Late Professor and Head of Department of Otolaryngology, University of Illinois, Chicago, and Howard Charles Ballenger, M.D., F.A.C.S., Associate Professor of Otolaryngology, Northwestern School of Medicine, Chicago. Cloth. Price \$12.00. Pp. 975, with 604 illustrations. Philadelphia, 1943, Lea & Febiger.

**NEUROSURGERY AND THORACIC SURGERY.** By Military Surgical Manuals, National Research Council. Cloth. Price \$2.50. Pp. 310, with 97 illustrations. Philadelphia, 1943, W. B. Saunders Company.

**SURGERY CLINICS OF NORTH AMERICA.** By many contributors. Cloth. Pp. 312, with 77 illustrations. Philadelphia, 1943, W. B. Saunders Company.

**GYNECOLOGY INCLUDING FEMALE UROLOGY.** By Lawrence R. Wharton, Ph.B., M.D., Associate in Gynecology, The Johns Hopkins Medical School; Assistant Johns Hopkins. Cloth. Pp. 1006, with 444 illustrations. Philadelphia, 1943, W. B. Saunders Company.

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### To Our Readers

The exigencies of the war situation have made it necessary to comply with the order of the War Production Board to reduce the weight of paper previously used for the JOURNAL. While this change will not affect the printed page it will affect the quality of the halftone illustrations. We regret that we have no choice in the matter and would ask the forbearance of our readers. As soon as the restrictions are removed, we shall resume our practice of printing the JOURNAL on the previously employed heavier grade of paper.

THE C. V. MOSBY CO., PUBLISHERS.

# SURGERY

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## Original Communications

Society of University Surgeons, Chicago, Ill.

Feb. 11-13, 1943

### TOTAL GASTRECTOMY; EFFECTS UPON NUTRITION AND HEMATOPOIESIS

J. MATTHEWS FARRIS,\* M.D., HENRY K. RANSOM, M.D., AND  
FREDERICK A. COLLIER, M.D., ANN ARBOR, MICH.

(From the Department of Surgery, University of Michigan)

**T**OTAL gastrectomy implies the complete removal of the stomach with a segment of the esophagus and duodenum. Connor<sup>7</sup> performed the first total gastrectomy upon man in 1884. His patient did not survive the operation. Thirteen years later, Schlatter<sup>27</sup> reported the first successful case. In the years that have followed little enthusiasm was shown for what has generally been considered a formidable procedure. The mortality rate was 50 per cent (eighty-eight cases collected by Roeder, in 1933). The implication that the patient might survive the operation only to be relegated to a life of invalidism has further deterred surgeons from accepting this procedure in the treatment of gastric neoplasms. It was first thought that following this operation the patient would be forced to subsist on predigested foods and others have predicted that pernicious anemia would be an invariable sequel.

Recent reports<sup>1, 2, 6, 8, 14, 17, 18, 20, 23, 33</sup> indicate that the operation is now being performed with increasing frequency. It is therefore apparent that a knowledge of the effect of total gastrectomy upon nutrition and hematopoiesis is of practical importance.

Few studies have been made on digestion in man after gastrectomy and the findings have been conflicting.<sup>12, 13, 15, 30</sup> Since 1937, twenty-nine complete gastrectomies have been performed at the University of Michigan Hospital. Twenty-four of these patients survived the operation and have provided an opportunity for observations of the essential

\*Captain, Medical Corps, U. S. Army.

Presented at the meeting of the Society of University Surgeons, Chicago, Ill., Feb. 11-13, 1943.

roles of the stomach in man. It is surprising how little their lives have been changed. A recent communication received from one of them reads: "I have continued to gain strength and have now gained thirty-three pounds. I am able to eat everything and am no longer troubled with indigestion."

This patient was operated upon Aug. 30, 1940, for an adenocarcinoma of the cardiac end of the stomach and was well thirty months later. Another patient, in his third postoperative year, was recently hospitalized for metabolic studies. He had gained twenty pounds and was able to take a 2,500 calorie diet in three regular meals without discomfort. There are several others who eat with little restriction in quantity or quality. Troublesome symptoms occurring early in the convalescence are related to the quantity of food ingested. These symptoms usually diminish rapidly as the postoperative period progresses. One patient, followed for nearly five years (longer than any case previously reported), is in good nutrition and has an excellent prognosis. Her case history follows.

R. B., a woman aged 40 years, was admitted to the University Hospital June 10, 1938. Her complaints were related to three episodes of hematemesis, melena, headache, weakness, and palpitation. She had been well until fifteen months prior to admission when she had experienced rather sudden vomiting of large amounts of grossly bloody material without premonitory signs. A second similar experience did not follow until nine months later during which time the patient had been quite well. Recovery was spontaneous and she was getting along well until three weeks prior to admission when the third episode supervened. Following this attack there were residual weakness, palpitation, and shortness of breath. There were few symptoms to suggest peptic ulcer and the patient had been able to tolerate all foods. There was no weight loss.

The physical examination revealed no abnormality other than a nodular enlargement of the fundus of a soft, movable uterus.

The laboratory findings were as follows: Hemoglobin (Sahli), 58 per cent; R.B.C., 4,400,000; W.B.C., 6,700; Kahn (blood), negative; serum proteins—total, 4.9; albumin, 3.0; globulin, 1.6.

TABLE I  
GASTRIC ANALYSIS WITH HISTAMINE

	FREE	COMBINED
Fasting	22	8
15 min.	16	8
30 min.	31	6
45 min.	28	6
60 min.	32	6

*Roentgenographic Examination.*—Eight serial films demonstrated a filling defect, presumably neoplastic in origin, involving the lesser curvature and upper portion of the body of the stomach. One large fleck was interpreted as ulceration within the neoplasm (Fig. 1).

*Peritoneoscopic examination* was carried out June 15, 1938. Observations were excellent. There was no evidence of carcinomatosis, ascites, or hepatic metastases. The gastric neoplasm could not be seen with transillumination of the stomach. A large fibroid was visualized on the anterior wall of the uterus. Five days were then



spent in preparing the patient for operation. The hypoproteinemia was corrected with transfusions of blood. The stomach was carefully washed daily, vitamin supplements and hydrochloric acid were included in the diet, and measures were directed toward improvement of oral hygiene. Operability of the lesion seemed quite dubious.

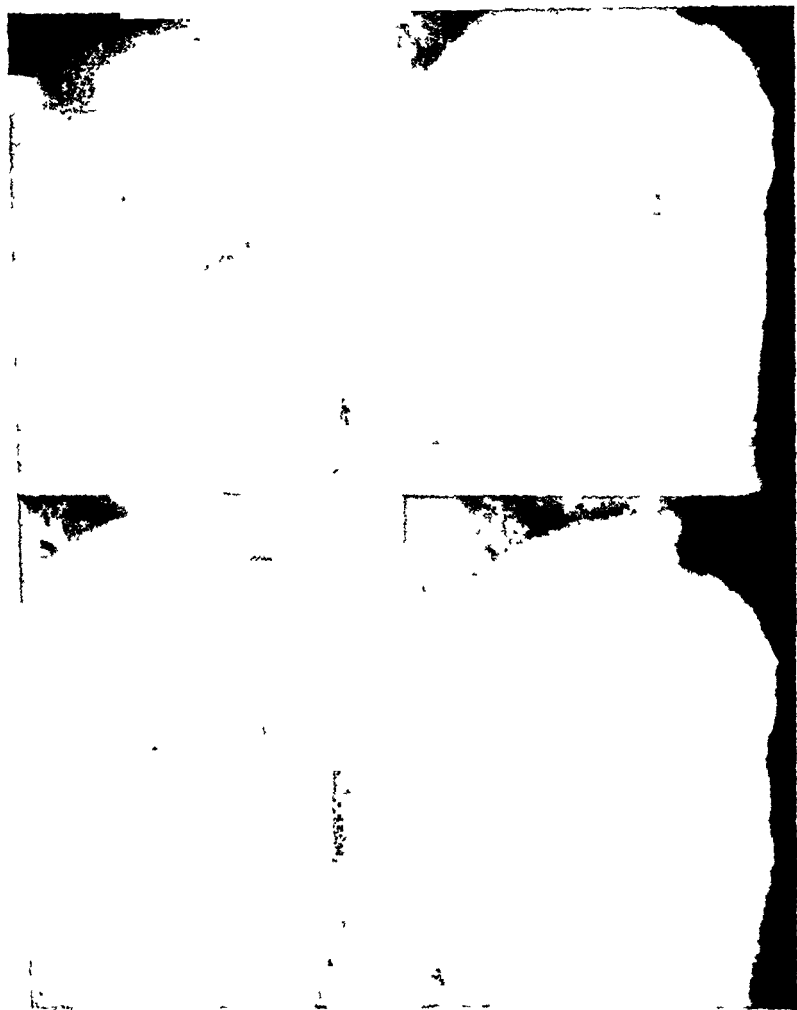


Fig 1—Serial films demonstrate a constant filling defect in the proximal lesser curvature of the stomach. One large ulcer fleck is visualized indicating ulceration within a large gastric neoplasm.

**Operation.**—On June 20, 1938, under spinal anesthesia, operation was performed (H. K. R.). On the lesser curvature of the stomach, in proximity to the esophagus, a peculiar dumbbell-shaped mass could be palpated. The mass consisted of two portions measuring approximately 3 by 4 cm., and extended to within 1 or 2 cm. of the esophagus. There were no palpable regional metastases but the extensive involvement of the proximal stomach precluded a partial gastrectomy. A total resection was therefore performed. The blood supply was divided along both curvatures beginning at the duodenum and extending to the esophagus. The duodenum was then divided and the stomach drawn upward to produce traction upon the intra-

abdominal esophagus. A loop of proximal jejunum was brought up through the transverse mesocolon and an esophagojejunostomy completed with two layers of interrupted fine silk sutures. The esophagus was not transected until the first row of sutures was in place. The peritoneum of the under surface of the diaphragm was utilized in buttressing and reinforcing the anastomosis. A complementary enteroenterostomy was made approximately 8 cm. below the previous anastomosis. A jejunostomy tube was placed in the efferent loop just below the mesocolon and brought out through a stab wound, lateral to the midline incision. The patient left the operating room in good condition and reacted promptly after returning to the ward.

*Pathologic Diagnosis.*—"A large neurofibroma of Schwannoma type. It is a well encapsulated, expansively growing neoplasm. The neoplasm will recur if not entirely removed." (Dr. C. V. Weller.)

*Postoperative Course.*—The patient's condition was excellent at all times. Jejunostomy feedings were begun after twenty-four hours and the patient was allowed up on her fourteenth postoperative day. The enterostomy healed promptly after removal of the tube. X-ray examination, on July 12, 1938, showed a satisfactory anastomosis between the esophagus and jejunum. She was living and well 56 months after operation.

In May of 1942 (at the end of the fourth postoperative year) a series of metabolic studies were begun using this patient as a subject.

*Metabolism of Protein and Fat Following Total Gastrectomy.*—She was placed on a weighed diet which was given for a three-day period (nine meals). The first and the ninth meal were "tagged" with carmine given orally. Collection of the feces was begun when the dye first appeared in the stool and stopped at the second appearance of the dye. The three-day collection was then dried and total nitrogen and total fat determinations were made.

The dry weight of the three-day stool was 62 Gm. and the total nitrogen content (Kjeldahl) was 2.34 Gm. The intake during the three-day diet had been carefully weighed and was as shown in Table II.

TABLE II  
INTAKE DURING THREE-DAY DIET

INTAKE	PROTEIN (GM.)	FAT (GM.)	CARBOHYDRATE (GM.)
1st day	68	89	250
2nd day	70	105	250
3rd day	62	72	235
Total	200	266	735

Most of the nitrogen arising from the catabolism of protein is excreted in the urine. A small fraction is eliminated through the secretion of the intestinal mucosa. This is *metabolic nitrogen* and may be estimated from the nitrogen of the feces on a nitrogen-free diet. In man 0.5 to 1.5 Gm. are excreted in this way daily. In order to determine the proportion of a given amount of protein which has undergone digestion and absorption, the total nitrogen content of the ingested protein is determined and the following formula used:

$$\text{Food Nitrogen} - (\text{Stool N} - \text{Metabolic N}) = \text{Absorbed Nitrogen}$$

The percentage of absorbed nitrogen is known as the *coefficient of digestibility*. The proteins of food contain 16 per cent nitrogen. Therefore, the 200 Gm. of ingested protein over the three-day period contained 12.5 Gm. of nitrogen. Employing this formula:

Food Nitrogen	Stool N	Metabolic N	Absorbed N
$\frac{200}{16} = 12.5$	(2.34)	1.0)	= 11.6 Gm.

The coefficient of digestibility of the protein in the three-day diet is 89.2 per cent. Of the various proteins those of animal origin are the most digestible (95 per cent). The digestibility of the protein in fruits and nuts is low and that of the proteins of legumes and of potatoes is around 80 per cent. The coefficient of 89.2 per cent is a normal figure for the protein contained in this diet.<sup>4</sup>

These results serve to support the clinical observation that patients are able to keep in good nutrition following total gastrectomy. As far as protein digestion is concerned it appears that the stomach does not play an essential role and this function may adequately be taken over by the trypsin of the pancreas and the erepsin of the small intestine.

This patient ingested 266 Gm. of fat in the three-day period. Total fat determinations (Saxlet) were done. There were 4.5 Gm. of total fat or 7.3 per cent of the dry weight. According to Bodansky and Bodansky<sup>3</sup> this value falls within the normal range of percentage of fat in dry feces. These findings are in accord with the general knowledge that gastric lipase is a weak fat-splitting enzyme, of little practical importance in adults. It is soon rendered inactive as the acidity of the gastric contents rises during digestion and any action it may have is exerted only upon fats in a state of very fine emulsion. Many question if this enzyme in the stomach has any real digestive value. Therefore, it is not surprising that complete gastrectomy does not interfere with this particular phase of nutrition.

Gavrila and Danicico,<sup>13</sup> from their study of thirteen patients upon whom gastroenterostomy and various types of *partial* gastrectomy had been performed, report that the digestion of fat was impaired in all the patients. They attributed this deficit to a pancreatic insufficiency following partial resection of the stomach. The increased motility of the gastrointestinal tract early in the postoperative period appears to be a much more likely cause. In nearly all cases of resection of the stomach the passage of food may be greatly accelerated early in the patient's convalescence. In four patients that we have followed for several years there have been no errors in fat metabolism.

*Hematopoiesis Following Total Gastrectomy.*—It is increasingly apparent that gastrectomy may be performed without any great fear of undue consequences as far as the factor of hematopoiesis is concerned. Fig. 2 shows the results of complete blood examinations over a four-year period following complete gastrectomy. The mean corpuscular volume has consistently remained below macrocytic levels. The original hypothesis of Castle implied that gastrectomy might well be followed by pernicious anemia. However, clinical experience indicates that this

complication is rarely, if ever, encountered. Furthermore, many experiments have been performed on a wide variety of laboratory animals in an effort to produce pernicious anemia of agastric genesis. No one has been able to produce the typical changes in the bone marrow and peripheral blood associated with hyperchromic macrocytic (pernicious) anemia following total gastrectomy in animals. The experiments of: Mann (1929), Ivy, Morgan, and Farrell (1931), Mann and Graham (1932), Aron and Bauer (1933), Mullenix, Dragstedt, and Bradley (1933), Douleine and Bondarenko (1934), Ducuing, Miletzky, and Soula (1936), Shumacker and Wintrobe (1935), Petri and Jensenius (1941), Singer (1935), Kohno (1935) have all given similar results in this regard.

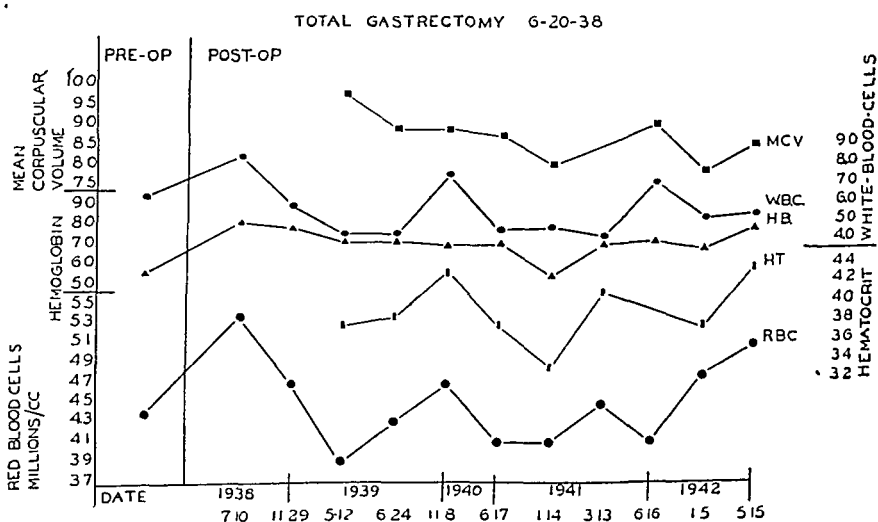


Fig. 2.—Illustrating blood findings over a four-year period. The mean corpuscular volume has consistently remained below macrocytic levels. Values between 110 and 140 are generally obtained in pernicious anemia. Low hemoglobin levels have invariably been associated with the failure to take ferrous iron. Elevation in hemoglobin level has been a consistent response to the administration of iron.

From a study of 800 partial gastrectomies, Walton<sup>12</sup> was unable to detect alterations in hematopoiesis. Sturgis and Goldhamer<sup>31</sup> were unable to collect more than three cases of macrocytic anemia following gastrectomy from the total group of anemias seen at the Simpson Memorial Institute at the University of Michigan. In our series of twenty-nine total gastrectomies, four have now survived the operation longer than two years. Careful blood examinations on these four patients do not show macrocytic anemia. However, many of the patients do develop an anemia although of the hypochromic microcytic type that is commonly associated with iron deficiency. Improvement is consistently apparent from the administration of hydrochloric acid with the diet or ferrous iron. The hemoglobin level will remain satisfactory as

long as the patient takes ferrous iron one week out of each month. Late in 1940, iron was not taken by this patient (Fig. 2) for two months and on Jan. 14, 1941, the hemoglobin level was 56 per cent (Sahli). However, when iron therapy was resumed, a satisfactory response was obtained.

This iron deficiency anemia results from alterations in the physiologic principles controlling the absorption of iron. Under normal conditions, the inorganic iron of the food which is in the ferric state, is converted by the HCl to the ferrous form. Ferrous iron is the only form in which it can be absorbed by the alimentary tract.<sup>4</sup> It is likewise now known that the organic form of iron in foods is not available for absorption as it is not released by peptic or tryptic ferments. Animals fed dipyriddy, for example, become anemic since the inorganic iron is rendered insoluble. In certain anemias accompanied by the absence of HCl, compounds of ferrous iron (sulfate, chloride, carbonate) are specific in their effects. It has been shown by Castle and associates that in hypochromic anemia a daily dose of 32 mg. of iron and ammonium

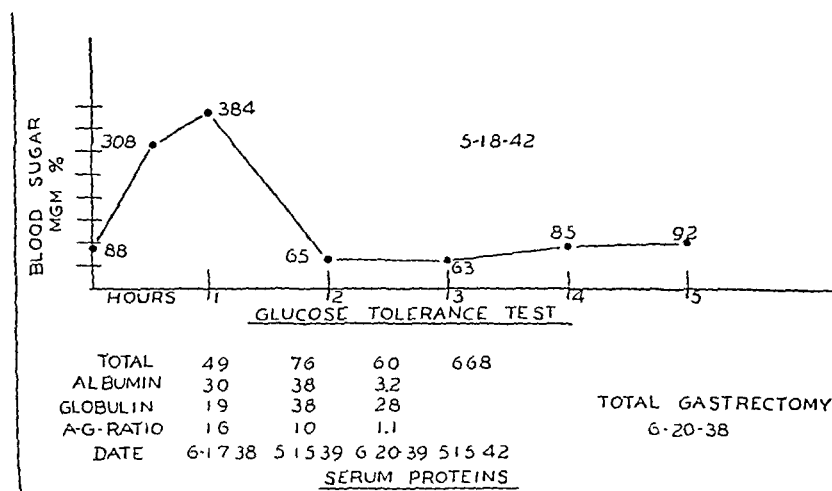


Fig. 3.—Illustrating glucose tolerance curve following total gastrectomy. These curves differ from normal in certain respects. The initial phase of hyperglycemia is more pronounced and has been followed in the cases studied by a rapid fall to levels approaching hypoglycemia. The lowest levels are usually observed in the third hour and are followed by gradual recovery to fasting levels in the fourth and fifth hours.

citrate, administered subcutaneously, is utilized completely in the formation of hemoglobin. It was also shown that 32 mg. of iron administered in this way is equal to 1,000 mg. given by mouth.<sup>4</sup> This further demonstrates that only a very small proportion of ferric iron is converted into the absorbable (ferrous) form in the alimentary tract under normal conditions. Therefore, after total gastrectomy, the inorganic iron normally contained in the richly iron-containing foods is not available for absorption until it has been changed into the ferrous form. This requires the presence of the hydrogen ion. Hydrochloric acid may be

given with the diet. In most of our patients, 0.32 Gm. of ferrous sulfate taken three times a day for one week out of each month has proved to be efficacious in preventing a hypochromic microcytic anemia.

**Carbohydrate Metabolism.**—Qualitative information concerning carbohydrate metabolism may be obtained from glucose tolerance studies. (Glucose tolerance curves following total gastrectomy differ from normal values in the following respects: The initial phase of hyperglycemia is more pronounced and has been followed in the cases studied by a rapid fall to hypoglycemic levels. The lowest levels of blood sugar have been observed during the third hour and are usually followed by a gradual recovery to fasting levels in the fourth and fifth hours (Figs. 3 and 4). These changes may be attributed to alterations in absorption, utilization or rate of deposition of glucose. Inasmuch as the *intravenous* glucose tolerance test in these patients gives a perfectly normal curve, it is apparent that these changes are a result of an increase in rate of absorption of glucose following total gastrectomy.

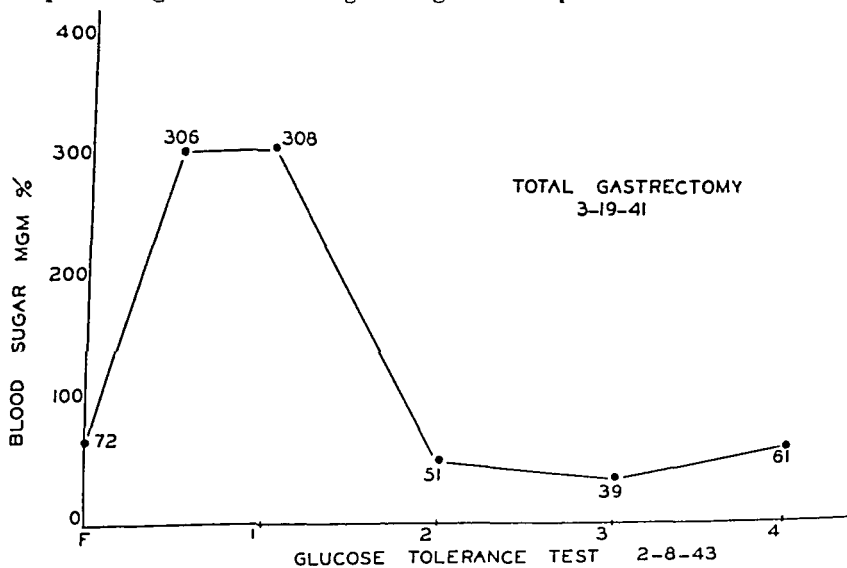


Fig. 4.—Illustrating hypoglycemia occurring during a glucose tolerance study (1.75 Gm. per kilogram of ideal body weight given orally). During the third hour the patient experienced definite symptoms of hypoglycemia.

It is noted in Fig. 4 that this patient's blood sugar was 39 during the third hour. This approaches convulsive levels and the patient was distinctly uncomfortable. These low blood sugar values may produce the typical signs of the hypoglycemia syndrome. It is presumably due to hyperinsulinism, which is secondary to the primary phase of hyperglycemia. This physiologic mechanism might well explain attacks of weakness, vertigo, and palpitation occasionally observed following partial gastrectomy. Rapid emptying of the stomach through large anastomoses (Polya type) will facilitate the rapid absorption of glucose and

may be followed by secondary hyperinsulinism and hypoglycemia. High protein, low carbohydrate diets are effective in preventing postprandial abnormalities in the blood sugar levels.

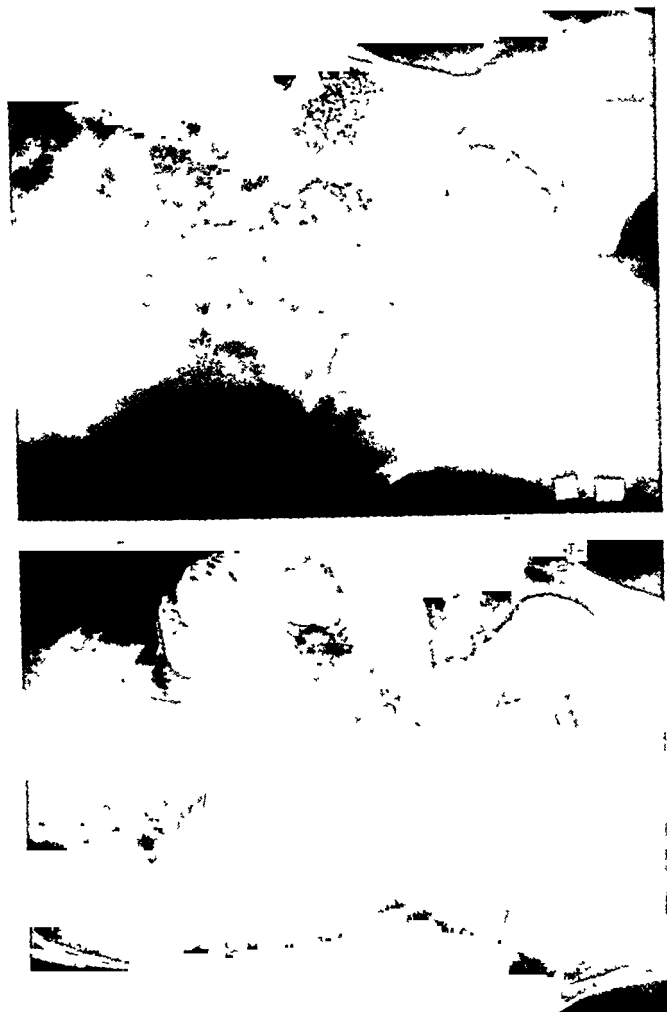


Fig. 5.—Roentgenograms after the ingestion of barium show enlargement of the distal jejunal loop (A). A five-hour film shows normal progression of the barium column through the small intestine (B). There is no evidence of barium in the colon examine administered orally does not appear in the stool for thirty-six hours.

*Motility of the Gastrointestinal Tract Following Total Gastrectomy.*—Gastroenterostomy, partial gastrectomy, and total gastrectomy may all produce transient increased motility of the gastrointestinal tract. Ingested powdered charcoal may appear in the stool in twelve hours.<sup>12</sup> When digestive deficits have been observed following gastric operation, it is reasonable to assume that they are a result of the increased motility. In the patients that we have followed, this phenomenon has been of temporary significance. Fig. 5A illustrates the changes occurring in the

distal loop of jejunum over a four-year period, following total gastrectomy. The storing capacity of the stomach is simulated. Fig. 5B illustrates the progress of the barium meal five hours after oral ingestion. There is no evidence of barium in the colon, which indicates a slight decrease in motility. Carmine administered orally does not appear in the stool for thirty-six hours. The vagus nerves are almost invariably sacrificed in the course of total gastrectomy. Inasmuch as they are predominantly motor, *gastrointestinal motility may eventually be decreased through this mechanism.* Another patient twenty-four months after operation showed progression of barium at one, three, and five hours, slightly slower than normal.

#### SUMMARY AND CONCLUSIONS

1. The mortality rate following total gastrectomy is not prohibitive. There have been two deaths in the last nineteen consecutive operations. One of these occurred in a man 79 years old.

2. The stomach does not play an essential role in the digestion of fats and protein.

3. There is no experimental evidence that removal of the stomach will produce pernicious anemia. Clinical experience likewise indicates that primary anemia is rarely encountered following various gastric operations.

4. Gastrectomy interferes with the metabolism of iron.

5. The absorption of glucose is more rapid than normal. This results in a transient hyperglycemia phase that is followed by hypoglycemia. This latter phase may produce characteristic symptoms. A high protein, low carbohydrate diet is efficacious in preventing these abnormalities.

6. A patient is reported who survived total gastrectomy four years and seven months. She is living and well.

7. Motility is decreased rather than increased. This may be due to intra-abdominal section of the vagus nerves.

We acknowledge the helpful collaboration of Miss Sue Biethan in preparing the bibliography.

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## INTESTINAL STRANGULATING OBSTRUCTION WITH NEGATIVE ROENTGENOLOGIC FINDINGS\*

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THE difficulties of recognizing internal intestinal strangulating obstruction are well known. Although the pain is usually colicky in nature, in some patients it is sharp and continuous, simulating that of perforated peptic ulcer, twisted ovarian cyst, acute pelvic inflammatory disease, or mesenteric infarction or thrombosis. The venous return from the segment of bowel is often occluded first so that the involved loop quickly fills with blood, usually replacing any gas which may be present in the affected loop. The physical findings in this group of patients simulate those of peritonitis rather than simple intestinal obstruction. The irritating serosanguineous fluid in the peritoneal cavity produces tenderness, rigidity, and an inhibition of peristalsis. While patients with acute strangulating intestinal obstruction may present symptoms closely resembling those of simple obstruction, the presence of fever, tenderness, rigidity, a palpable abdominal mass, or leucocytosis is usually evidence that the blood supply has been interrupted.

Since Schwartz,<sup>1</sup> Assmann,<sup>2</sup> Case,<sup>3</sup> and others emphasized the positive roentgenologic findings of intestinal obstruction, little has been mentioned about the possibility of negative findings, particularly in strangulating obstructions. Rabwin<sup>4</sup> mentioned two such patients in whom no evidence of obstruction appeared on x-ray examination.

We have observed several patients with minimal roentgenologic evidence of obstruction, characterized by the presence of a small accumulation of gas in the proximal bowel, even though several feet of small intestine were gangrenous. We have seen four patients with acute strangulating intestinal obstruction, two of whom showed no roentgenologic evidence of obstruction and two of whom showed changes which might be considered questionable. In the latter group such changes as appeared were thought to represent signs of paralytic ileus inasmuch as it was believed that peritonitis from some other cause might be present.

### CASE REPORTS

#### *Strangulating Obstruction With Negative Roentgenologic Findings*

CASE 1.—K. W., a housewife, 66 years of age, had had a hysterectomy ten years prior to the present illness. She presented a history of cramplike pain at the onset

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which quickly became continuous in type and spread over the entire abdomen. This was followed by constipation and the vomiting of bile-stained fluid. The physician in attendance observed her at home for twenty-four hours. On entry her temperature was  $37.5^{\circ}\text{C}$ ., pulse rate 110, respirations 24. The abdomen was tender and rigid throughout the lower portion and no peristaltic activity was heard. The blood count showed 92 per cent hemoglobin; red blood cells, 4,420,000; white blood cells, 14,600; polymorphonuclear leucocytes, 78 per cent. Her pain and findings increased. Thirty-six hours after the onset of her illness, roentgenograms of her abdomen showed the stomach and first portion of the duodenum to be distended with gas, but there was no evidence of gaseous distention of the small intestine (Fig. 1). At operation immediately thereafter, approximately four feet of gangrenous lower ileum were found. The strangulation was caused by a narrow adhesive band running from the posterior parietal wall on the right side to the region of the broad ligament. This band had tightly encased the bowel and its mesenteric blood supply, causing complete obstruction to both. The gangrenous loop of bowel was heavy, filled with sanguineous fluid, and there was a large amount of serosanguineous fluid in the peritoneal cavity.



Fig. 1.—Roentgenogram showing gas in the stomach and duodenum but none in the small intestine; four feet of gangrenous ileum were resected in this patient.

CASE 2.—B. S., a housewife, 44 years of age, had had an appendectomy through a right rectus incision fourteen years previously, and a right salpingo-oophorectomy eight years before this illness. Sixteen hours before entry to the hospital she had sudden, severe, progressive pain in the mid-portion of the abdomen. She vomited upper intestinal contents only once. On entry, her temperature was  $37.9^{\circ}\text{C}$ ., pulse rate 100, and respirations 20. The abdomen was not distended and a mass could be

outlined in the left lower quadrant. Mild tenderness and rigidity were present throughout the lower half of the abdomen and no peristalsis was heard. Blood count showed 78 per cent hemoglobin; red blood cells, 3,860,000; white blood cells, 18,600; polymorphonuclear leucocytes, 84 per cent; lymphocytes, 11 per cent; monocytes, 2 per cent. Shortly before operation a roentgenogram (Fig. 2) showed the presence of gas only in the large intestine. There was no evidence of distention or accumulation of gas or fluid in the small bowel. At operation a moderate amount of bloody fluid was found in the peritoneal cavity. A very tight adhesive band ran from the mesentery of the terminal ileum to the left parietal wall and completely constricted the lumen of the bowel and its blood supply. Approximately five feet of gangrenous lower jejunum and upper ileum were resected.



Fig. 2.  
of the small  
encounter

gas present in the colon; there is no distention  
five feet of gangrenous jejunum and ileum were

#### *Strangulating Obstruction With Questionable Roentgenologic Findings*

CASE 3.—O. C., a woman, 48 years of age, had had a right salpingo-oophorectomy and appendectomy sixteen years previously. She entered the hospital after twenty-eight hours of severe pain, which was colicky at the onset but soon became continuous in character. She vomited several times and had one small normal bowel movement. Her temperature was 38.4° C., pulse rate 120, respirations 24. The abdomen was slightly distended and peristalsis diminished. A mass palpated in the lower abdomen on bimanual pelvic examination was thought to be an ovarian cyst twisted on its pedicle. The blood count showed 96 per cent hemoglobin; red blood cells, 4,640,000; white blood cells, 22,400; polymorphonuclear leucocytes, 92 per cent; lymphocytes, 8 per cent. The roentgenogram (Fig. 3) showed evidence of gas in the stomach,

duodenum, splenic flexure, and sigmoid colon. A centrally placed loop of bowel showed a small amount of gas running transversely. These findings were interpreted as being consistent with paralytic ileus and the grayness of the film suggested free fluid. Laparotomy showed a large amount of bloody fluid in the peritoneal cavity. An adhesive band running between the mesenteries of the loops of small intestine had caused the strangulation of six feet of ileum.



Fig. 3.—Roentgenogram interpreted as showing no evidence of mechanical obstruction. Six feet of ileum were strangulated by adhesive band.

CASE 4.—L. L., a man, 34 years of age, had had an appendectomy through a right rectus incision six years previously. Twelve hours before entry to the hospital, severe colicky pain began in the right lower quadrant followed by vomiting and constipation. His temperature was  $38.5^{\circ}$  C., pulse rate 110, and respirations 28. The abdomen was not distended, slight guarding and tenderness were present over the right side. Peristalsis was hyperactive, the sounds being high-pitched and metallic. Blood count showed 90 per cent hemoglobin; red blood cells, 4,620,000; white blood cells, 17,600; polymorphonuclear leucocytes, 85 per cent; lymphocytes 12 per cent. Roentgen examination (Fig. 4) showed gas in the stomach and colon. There was a loop of gas filled bowel along the left lateral wall which was interpreted as being descending and sigmoid colon. At operation, eighteen inches of gangrenous lower jejunum were found, having been produced by an adhesive band. A moderate amount of bloody free fluid was encountered.

The interest aroused by these cases, with few or no roentgenologic evidences of obstruction in the plain film, stimulated experimental work in an attempt to explain its mechanism.

In 1933, Ochsner,<sup>5</sup> after tightly ligating loops of small intestine together with their blood supply, in dogs, reported that strangulating obstruction produced more marked accumulations of gas and fluid than were found in simple obstruction, and noted that the roentgenologic findings appeared earlier than in the simple type. Goehl, Lynch, Borman, and Wangenstein,<sup>6</sup> on the other hand, observed that roentgenologic evidence of intestinal obstruction did not appear so early in animals with strangulation as in those with simple obstruction. The same method of ligation as that employed by Ochsner was used, except

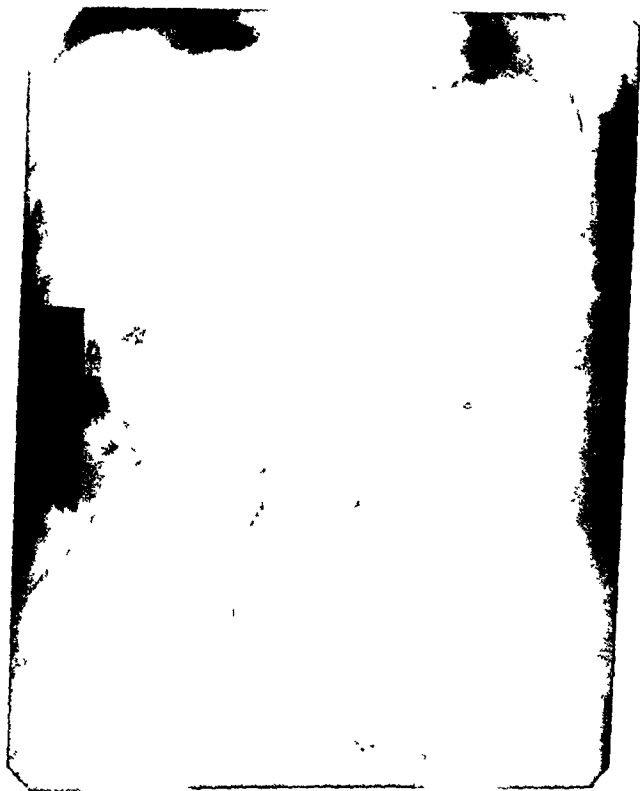


Fig. 4—Roentgenogram showing questionable loop of distended small bowel or colon in the left flank. Eighteen inches of lower jejunum were strangulated by adhesion.

that varying degrees of strangulation were obtained. Carlson, Dvorak, Lynch, Borman, and Wangenstein,<sup>7</sup> after ligations of mesenteric vessels in dogs, concluded that, while roentgenographic evidence of gaseous distention is an early and a valuable sign of simple intestinal obstruction, it is of distinctly less value in strangulating obstruction or stasis caused by occlusion of the mesenteric vein. Hibbard, Swenson, and Levin<sup>8</sup> were unable to produce positive roentgenologic findings of obstruction after ligating mesenteric veins which drain long segments of small intestine. X-ray films taken after ligation of the superior mesenteric vein

draining one-half of the ileum and jejunum did not reveal the presence of gas, whereas films taken after the ligation of the mesenteric veins draining nearly 10 cm. of the ileum showed the presence of gas in three hours and fluid in five hours. In studying mesenteric occlusion as well as intestinal strangulation numerous observations have been made<sup>3</sup> on the effects of the ligation of arteries, veins, both arteries and veins, and the wall of the bowel, in various combinations.

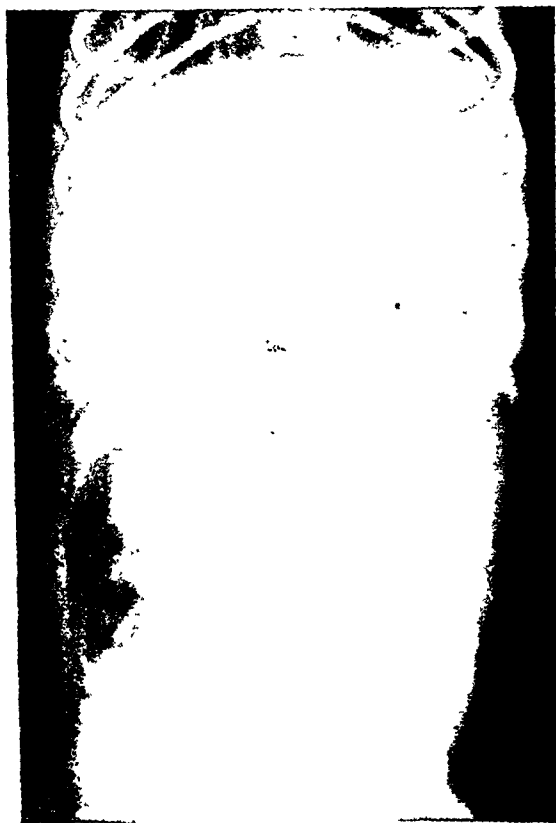


Fig. 5—Roentgenogram showing gaseous distention of small intestine of dog following ligation of a segment of ileum and its blood supply.

#### EXPERIMENTAL METHODS

It occurred to us that, in order to simulate more closely the mechanism of internal strangulating obstruction caused by the slipping of a loop of bowel under a band or through an abnormal opening, in the human being, the gradual production of strangulation might be preferable to ligation. The changes occurring when a loop of intestine and its blood supply are gradually constricted are venous engorgement, perivascular hemorrhage, venous stasis, edema, cyanosis, spasm of the affected loop of bowel, and hemorrhage into the lumen and the wall of the bowel. The mesentery becomes edematous so that the arterial

In 1933, Ochsner,<sup>5</sup> after tightly ligating loops of small intestine together with their blood supply, in dogs, reported that strangulating obstruction produced more marked accumulations of gas and fluid than were found in simple obstruction, and noted that the roentgenologic findings appeared earlier than in the simple type. Goehl, Lynch, Borman, and Wangenstein,<sup>6</sup> on the other hand, observed that roentgenologic evidence of intestinal obstruction did not appear so early in animals with strangulation as in those with simple obstruction. The same method of ligation as that employed by Ochsner was used, except

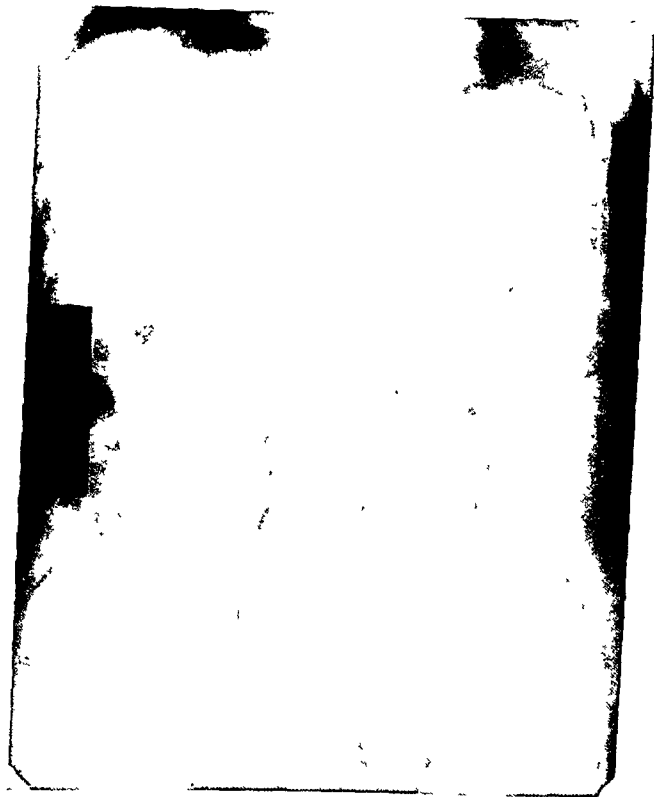


Fig. 4.—Roentgenogram showing questionable loop of distended small bowel or colon in the left flank. Eighteen inches of lower jejunum were strangulated by adhesion.

that varying degrees of strangulation were obtained. Carlson, Dvorak, Lynch, Borman, and Wangenstein,<sup>7</sup> after ligations of mesenteric vessels in dogs, concluded that, while roentgenographic evidence of gaseous distention is an early and a valuable sign of simple intestinal obstruction, it is of distinctly less value in strangulating obstruction or stasis caused by occlusion of the mesenteric vein. Hibbard, Swenson, and Levin<sup>8</sup> were unable to produce positive roentgenologic findings of obstruction after ligating mesenteric veins which drain long segments of small intestine. X-ray films taken after ligation of the superior mesenteric vein





Fig. 7B.



Fig. 7A

Fig. 7A — Photograph showing a loop of gangrenous ileum and proximal bowel for comparison

Fig. 7B — Roentgenogram showing absence of gaseous distention, note the accumulation of fluid in the exteriorized loops

supply is also encroached upon at the neck of the constriction and the lumen of the bowel is occluded, thereby setting up a vicious cycle, until perforation and peritonitis take place or sufficient hemorrhage accumulates in a long segment to be an added factor in causing shock or death.

Accordingly, three groups of experiments (ten dogs each) were carried out in an attempt to determine the frequency of negative x-ray findings in strangulating obstructions.



Fig. 6—Drawing showing method of producing gradual strangulating obstruction

*Group 1.*—A loop of ileum, 40 cm. in length, with its blood supply, was ligated with stout cotton tape, approximately 75 cm. proximal to the ileocecal valve so as initially to occlude the lumen and its mesenteric circulation. This was carried out in an aseptic manner under ether anesthesia and the operative wound was closed. Anteroposterior films were then taken with the animal held at 60 degrees of the vertical position.

*Results:* In all of these dogs roentgenograms showed evidence of accumulation of gas and fluid proximal to the strangulation (Fig. 5) within ten hours, the earliest appearing at 2½ hours and the average

average being  $3\frac{3}{4}$  hours. Anteroposterior x-ray films were taken within from 6 to 10 hours. Seven of the animals showed definite accumulations of gas as seen by the x-ray. In 3, however, no gaseous accumulation or distention was noted proximally to the obstruction. Fig. 7A shows a loop of gangrenous bowel produced in this manner and the immediately proximal loop placed cephalad for comparison. The collapsed state of the proximal loop of bowel can be noted and compared to the x-ray film (Fig. 7B) of this same animal which discloses no gaseous distention proximal to the obstruction. Great venous engorgement and tenseness, and gangrene of the involved loop are evident.

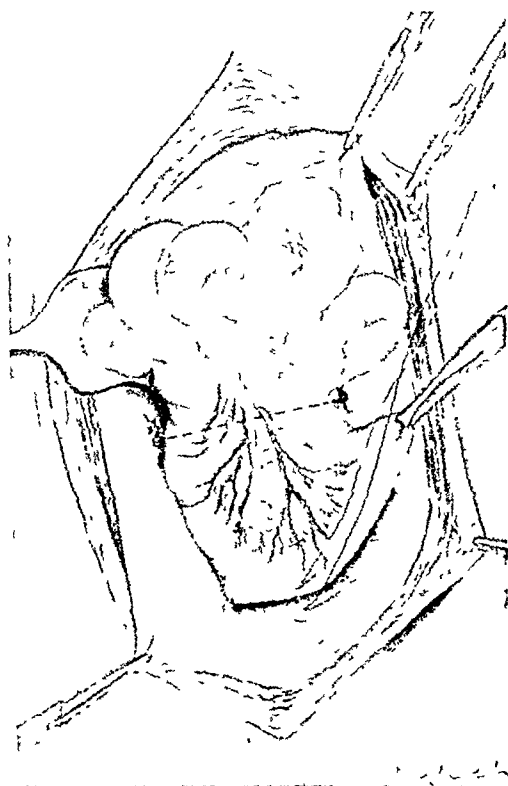


Fig. 8B

*Group III.*—In order to produce intestinal strangulation in this manner but carry the observations over a longer period of time, the same effect was produced in 10 dogs by placing a similar loop of ileum over a stout linen suture, running transversely across the peritoneal cavity and anchored at the lateral border of the rectus sheath on each side (Figs. 8A, 8B, and 8C). This was done under ether anesthesia, with aseptic technique. The loop of ileum was then sutured to the retroperitoneal fascia anterior to the sacrum so that there would be no later

being approximately 6 hours. In all of the animals autopsies revealed distention due to the accumulation of gas and fluid proximal to the obstruction.

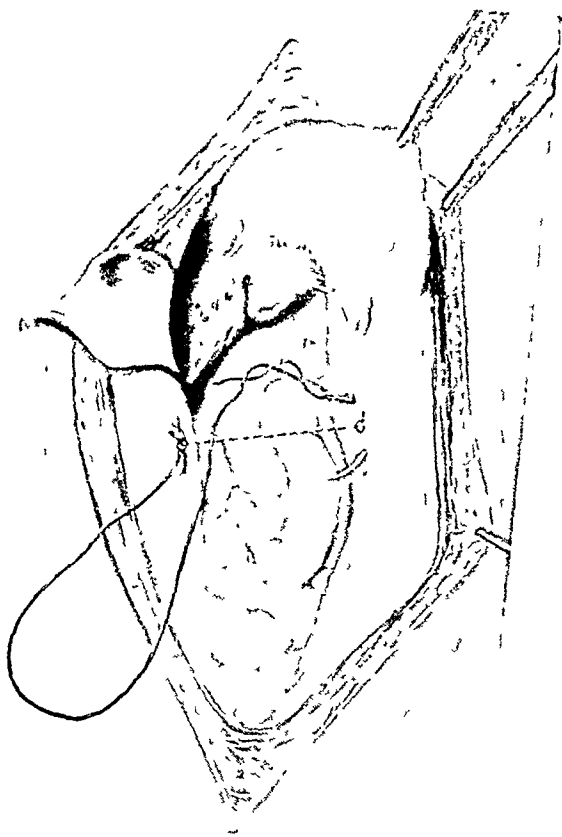


Fig. 3.—A, B, and C Drawings showing the method of producing gradual strangulation aseptically

*Group II.*—Under intravenous sodium pentobarbital anesthesia, supplemented as needed, a loop of ileum 40 cm. long with its mesentery was exteriorized over a linen string, the height of which could be regulated above the level of the anterior abdominal wall (Fig. 6). The loop of intestine was permitted to hang apronlike over the string onto the lower portion of the anterior abdominal wall. The height of the string was then adjusted to a level that would produce venous engorgement. The bowel was handled gently and kept warm with pads so as to minimize the inhibition of peristalsis as much as possible. This loop was observed as long as the dog could be prevented from going into shock, a period varying from 6 to 12 hours.

*Results:* In some of the dogs the arterial pulsations to the loops disappeared within 2½ hours and in some they continued for 6 hours, the

of the animals in which the occlusion was produced in such a manner as to permit intestinal obstruction to occur gradually. This may be explained (1) as a chance finding, although the animals in Group I, which may be considered controls, all had positive x-ray evidence of obstruction; (2) it is possible, however, that mesenteric venous occlusion causes a state of gangrene to occur before the lumen of the bowel is



Fig 9—Roentgenogram showing absence of gaseous distention in dog in which strangulation obstruction had been produced.

obstructed; (3) this occlusion may provoke a profusion of irritating serosanguineous fluid causing an inhibition of peristalsis and signs of peritonitis so that the x-ray films suggest adynamic ileus or no findings at all; (4) the irritative effect of a band or hernial ring may, by damage to the intima, initiate a venous thrombosis as is produced by simple ligation of a blood vessel.

#### SUMMARY

1. Two cases of internal strangulating obstruction and gangrenous bowel without x-ray evidence are reported.
2. Strangulating obstruction may be present with x-ray films suggesting adynamic ileus.

displacement. It was placed under sufficient tension that the string would cause engorgement of the venous return.

*Results:* The x-ray films of eight of the ten dogs showed evidence of obstruction as characterized by gaseous distention of the small bowel.

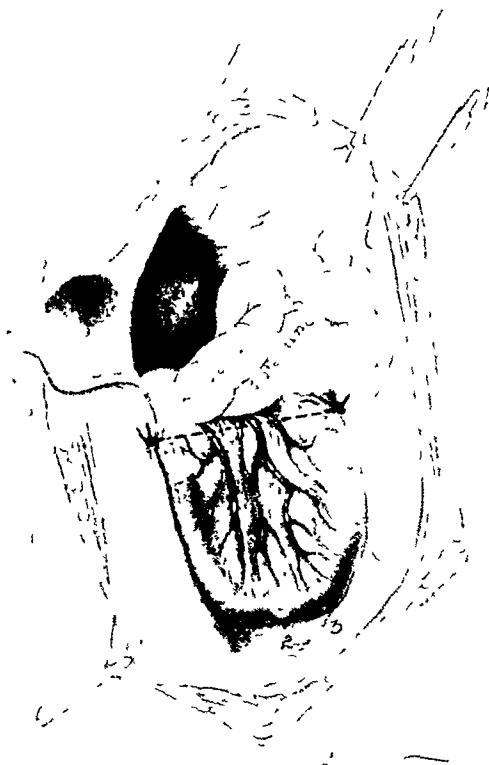


Fig. 8C.

These findings were noted at 6 hours in two of the animals, at 12 hours in three, and at 18 hours in three. Roentgenograms of the other two dogs showed no gaseous distention after 28 hours (Fig. 9). The bowel was gangrenous and autopsy disclosed thrombosis of the involved mesenteric veins. Experiments were not included if gangrenous changes were absent.

#### DISCUSSION

In order to simulate more closely the findings of strangulating obstruction as seen in our patients, experiments were carried out which brought about a gradual strangulation and obstruction of the lumen of the bowel. Gaseous distention may not occur in experiments such as those cited above which produce occlusion of the mesenteric vessels as in clinical mesenteric thrombosis, particularly of the venous type. Roentgenologic evidences of obstruction were absent in from 20 to 30 per cent

## EXPERIMENTAL STUDIES OF THE VALUE OF SULFATHIAZOLE IN PERITONITIS\*

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THE bacteriostatic activity of the sulfonamides has been demonstrated repeatedly both by well-controlled experiments and by the accumulation of clinical observations. The exact mode of action may still be conjecture and a correct understanding of this action may not have been proposed, but the practical observation that these compounds have a highly selective inhibitory effect on the metabolic processes of bacterial reproduction seems well founded. The entire concept of cellular growth and drug action may well be influenced by the studies which have been stimulated in this field.

The use of the sulfonamides locally in the peritoneal cavity has been the natural outgrowth of the first favorable report on the local, bacteriostatic effect by Sinclair and Barker (1937).<sup>1</sup> No attempt will be made to review the past work in this general field. A number of clinical observations have been published on the use of the sulfonamides both by systemic and intraperitoneal administration.<sup>2-6</sup> A lesser number of experimental observations on the local, intraperitoneal use of these substances have been reported.<sup>6-10</sup>

This study is an attempt to determine the relative values of systemic and local intraperitoneal administration of sulfathiazole in treating an experimentally produced peritonitis. In attempting to evaluate the relative effectiveness of a drug it is not necessary to reproduce a specific disease entity, but it is imperative to form a reproducible lesion of sufficient lethal effects to be significant and yet be amenable to treatment to the extent that differential effects to the various forms of treatment being studied can be observed. The preparation of such a test object, an open duodenojejunal loop, as indicated in Fig. 1, seems to fulfill this requirement in that 100 per cent of the control animals died and in that certain forms of therapy protected 100 per cent of the treated animals for a significant period of time.

*Experimental Procedure.*—After withholding food for twenty-four hours, an upper midline incision was made under ether anesthesia and the duodenum was identified and divided (2 cm.) distal to the main

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3. In ten dogs the sudden production of strangulating obstruction to a loop of small intestine produced x-ray evidence of intestinal obstruction.

4. Gaseous distention was not observed in the roentgenograms of 25 per cent of the twenty dogs in which strangulating obstruction was produced by gradual interference with the blood supply and later with the wall of the bowel itself.

5. Clinical and experimental observations suggest that the absence of evidence of intestinal obstruction in plain roentgenograms may not rule out the likelihood of intestinal strangulating obstruction.

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Water was always available to the animals, but food was withheld for four days. Practically all of the animals vomited during the first few days following operation. Abdominal distension was seldom present, but muscular rigidity always existed for five to seven days postoperatively when survival occurred.

Ten cubic centimeters of blood were drawn daily for the determination of chlorides, nonprotein nitrogen, plasma protein, hemoglobin, and the concentration of sulfathiazole. These data are summarized in Tables 1, 2, 3, 4, 5, and 6, respectively, for Groups I, II, III, IV, V, and VI, of ten animals each. Routine autopsies were performed for gross observation and culture of abdominal contents.

Table 1—Group I; control series of animals Duodenojejunal segment washed with 10 cc of physiologically normal salt solution. \* See Key to Tables

Animal	D-176	D-177	D-178	D-179	D-180	D-181	D-182	D-183	D-184	D-185
Days of Survival	1½	2½	1½	3½	1	2	1½	3	2	1½
Initial Flora	Count	0	High	High	Low	0	High		Low	High
	Identity	A, P	A, B, C	A, B, G, I	A, B, K, M	A, B, D, R	None	A, C, E	A, B, P	A, C
Final (b) Flora	Count	Low	High	High	High	High	High	High	High	High
	Identity	A, P*	A, B, C	A, B, G	A, B, M	A, B, D, R	A, C	A, C, E	A, B, P	A, C
Blood Chloride	Initial	399	412	395	392	402	390	398	408	400
	Mgm %									
	Max.	399 <sup>2</sup>	412 <sup>1</sup>	395 <sup>1</sup>	392 <sup>1</sup>	402 <sup>1</sup>	390 <sup>1</sup>	398 <sup>1</sup>	408 <sup>1</sup>	400 <sup>1</sup>
	Min.	364 <sup>2</sup>	273 <sup>3</sup>	334 <sup>2</sup>	252 <sup>4</sup>	360	330 <sup>2</sup>	340	260 <sup>3</sup>	345 <sup>3</sup>
N.P.N.	Initial	20.1	34.5	32.7	20.9	25.6	27.4	26.8	24.3	31.3
	Mgm %									
	Max.	40.1 <sup>2</sup>	28.7 <sup>3</sup>	68.4 <sup>2</sup>	139.6 <sup>2</sup>	32.4	56.2 <sup>2</sup>	49.7 <sup>2</sup>	96.8 <sup>3</sup>	66.7 <sup>2</sup>
	Min.	20.1 <sup>1</sup>	34.5 <sup>1</sup>	32.7 <sup>1</sup>	20.9 <sup>1</sup>	25.6	27.4 <sup>1</sup>	26.8 <sup>1</sup>	24.3 <sup>1</sup>	31.3 <sup>1</sup>
Plasma Protein	Initial	6.35	5.65	6.29	5.70	5.83	6.12	5.92	6.21	5.88
	Mgm %									
	Max.	6.35 <sup>1</sup>	6.30 <sup>1</sup>	6.29 <sup>1</sup>	7.66 <sup>4</sup>	5.83	6.41	5.92	7.92 <sup>2</sup>	5.88 <sup>1</sup>
	Min.	6.17 <sup>1</sup>	5.65 <sup>1</sup>	5.73 <sup>1</sup>	5.35 <sup>2</sup>	5.72	6.12 <sup>1</sup>	5.71 <sup>1</sup>	6.21 <sup>1</sup>	5.60 <sup>1</sup>
Hemoglobin	Initial	14.30	17.95	22.00	18.80	15.42	19.32	16.84	20.62	21.21
	Gms/100 cc									
	Max.	20.55 <sup>2</sup>	20.87 <sup>2</sup>	25.97 <sup>2</sup>	23.60 <sup>2</sup>	16.08	24.26 <sup>2</sup>	19.74 <sup>2</sup>	23.56 <sup>2</sup>	23.37 <sup>2</sup>
	Min.	14.30 <sup>1</sup>	17.95 <sup>1</sup>	22.00 <sup>1</sup>	18.80 <sup>1</sup>	15.42	19.32 <sup>1</sup>	16.84 <sup>1</sup>	20.62 <sup>1</sup>	21.21 <sup>1</sup>

Key to tables 1, 2, 3, 4, 5, 6.

(a) Initial Flora is the bacterial flora present in the segment at the time of operation (b) final Flora is the bacterial flora present in the segment and peritoneal cavity at exploration 4 weeks after operation or at autopsy if the animal died sooner than 4 weeks

Designation of Organisms A *C. welchii* B *B. coli* C. *alpha streptococcus fecalis* D *beta streptococcus* E *gamma streptococcus* F *Streptococcus liquefaciens* G *Salmonella* H *Staphylococcus albus* I *Staphylococcus aureus* J *B. subtilis* K *Diphtheroids* L *B. proteus* M *B. pyocyaneus* N *C. sporogenes* P *B. aerogenes* Q *B. alkaligenes* R *Neisseria flava*

Note The figures appearing as small superscripts indicate the day of the experiment on which the observation was made. In the bacterial counts 1cc corresponds to a count less than 1000. Average 10 000 to 100 000 High 1 000 000 or more

2, 3, 4, 5, and 6, respectively, for Groups I, II, III, IV, V, and VI, of ten animals each. Routine autopsies were performed for gross observation and culture of abdominal contents.

Group I.—Ten animals were subjected to the basic operation and served as controls. The average length of survival was two days. Al-

pancreatic duct. The jejunum was located and divided distal to Treitz ligament at a point permitting an end-to-end anastomosis to re-establish continuity of the gastrointestinal tract and isolate a segment of bowel approximately 20 cm. long composed of essentially equal lengths of duodenum and jejunum. The proximal end of this segment was closed by inversion (Fig. 1). This isolated loop was washed with 10 c.c. of

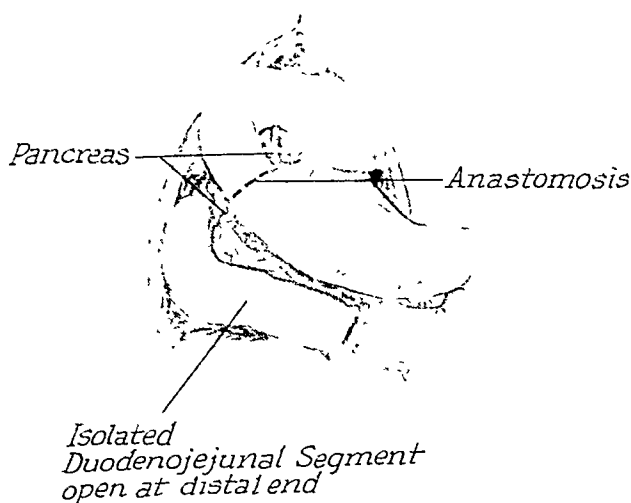
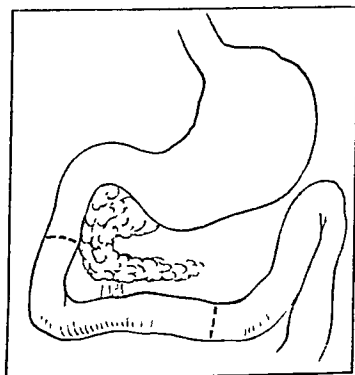


Fig. 1.—Illustrating the operation performed on all of the animals. The duodenum was divided about 2 cm. distal to the pancreatic duct, and the jejunum was divided below Treitz ligament so as to permit an end-to-end anastomosis of the proximal end of duodenum to re-establish continuity with the jejunum. An isolated segment comprised of approximately 10 cm. of each duodenum and jejunum resulted. The duodenal end of this segment was closed by inversion; the distal end was left open to communicate freely with the peritoneal cavity.

physiologically normal sodium chloride solution, and the washings were studied bacteriologically. The loop was dropped into the peritoneal cavity with its distal end open, and the abdomen was closed. This basic procedure was executed in all sixty animals included in this study.

The washings from the loop were exhaustively studied for total bacterial content and for the identification of both aerobic and anaerobic organisms.

subcutaneous dose of sulfathiazole which resulted in but a brief maintenance of a relatively low general systemic concentration of the drug. Twenty per cent of the animals lived more than 15 days. The changes in the composition of the blood were similar to those observed in Group I.

*Group III.*—One day preceding the usual operative procedures, these ten animals received 2.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, by subcutaneous injection at ten different sites. This procedure maintained a significant tissue level of sulfathiazole for approximately 10 days (Fig. 2). From the summarized data in Table 3 it was evident that less vomiting occurred post-operatively. This treatment conferred significant protection with 40 per cent of the animals living more than 15 days and an average survival period of 25.6 days for the entire group. Since the tissue was impregnated with sulfathiazole twenty-four hours before contamination of the peritoneal cavity, this group should represent the best results that can be expected from systemic treatment with sulfathiazole.

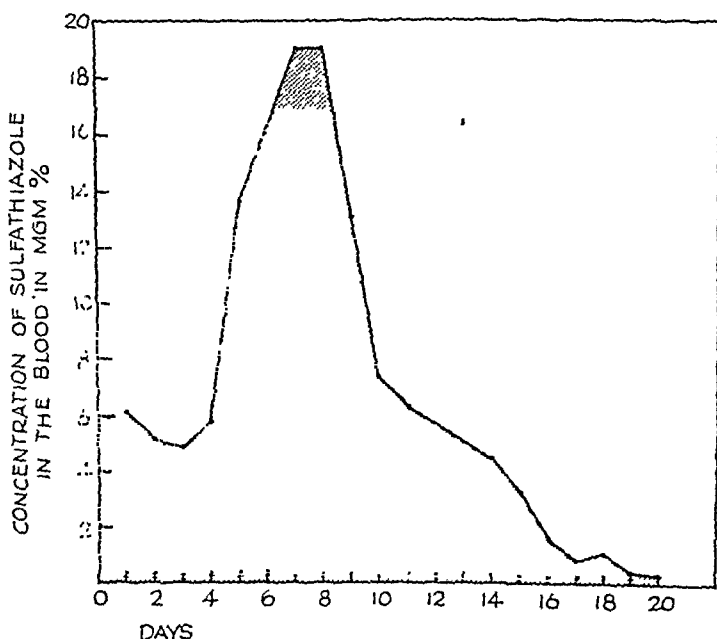


Fig. 2.—A characteristic chart of the concentration of sulfathiazole in the blood following the subcutaneous injection at ten different sites of a saline suspension of 2.5 Gm. of the drug per kilo of body weight.

*Group IV.*—At the time of the usual operation to form the duodeno-jejunal segment, 0.5 grams of sulfathiazole per kilo of body weight, suspended in normal salt solution, were injected into the general peritoneal cavity of ten animals. Sixty per cent of these animals survived more than 15 days and the average length of survival was 51.5 days. The concentration of sulfathiazole in the blood was appreciable for

though the survival was brief, the increase of hemoglobin and decrease in blood chlorides reflect the effect of postoperative vomiting resulting from the acute peritonitis which was evident at autopsy, Table 1.

Group II.—Immediately following the operation to form an isolated, open duodenojejunal segment each of ten animals received 0.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solu-

Table 2 Loop washed with 10 cc of physiologically normal salt solution 0.5 grams of sulfathiazole per kilo of body weight suspended in normal salt solution injected subcutaneously at a single site immediately following operation

Animal	D-132	D-133	D-134	D-135	D-153	D-170	D-171	D-172	D-173	D-174	
Days of survival	3½	2	2	2½	85	4	2	2½	3	20	
Bacterial Flora Initial	Count	Low	Average	Low	Average	0	Low	High	Average	Low	0
	Identity	A.B.J.L	A.B.J.L	A.H.K.L	A.B	None	A.B.C	A.B.G	A.B.J.K	A.C.	None
Bacterial Flora Final	Count	High	High	High	High	0	High	High	High	High	Average
	Identity	A.B	A.B.J.L	A.B	A.B	None	A.B	A.B.G	A.B.J.K	A.C	A
Blood Chlorides Mgm	Initial	395	390	409	392	403	404	396	389	406	410
	Max.	395	390	409	392	403	404	396	389	406	410
	Min.	358	362	394	348	342	310	370	351	321	362
NPN Mgm %	Initial	27.6	30.1	27.6	24.5	25.4	26.2	28.7	25.2	21.3	20.6
	Max	27.6	30.1	48.0	29.0	35.1	47.6	38.6	36.4	52.1	25.6
	Min	25.5	27.1	27.6	24.5	25.4	26.2	28.7	25.2	21.3	20.6
Plasma Protein %	Initial	5.75	5.97	5.85	4.93	5.27	5.42	4.96	5.38	5.88	5.78
	Max	5.75	5.97	5.85	6.58	6.46	6.82	5.36	5.38	6.20	6.10
	Min	4.88	5.45	4.11	4.93	5.27	5.42	4.96	4.82	5.88	5.20
Hemoglobin Gms/100cc	Initial	21.74	17.47	20.00	15.93	15.73	16.73	18.91	19.26	20.64	18.25
	Max	22.26	18.68	27.20	19.32	21.90	28.64	23.46	22.82	24.42	19.81
	Min	20.83	17.47	20.00	15.93	15.73	16.73	18.91	19.26	20.64	13.62
Blood Sulfathiazole Concentration Mgm	Day 1			0.97		1.08	1.26	1.14	1.32	0.94	1.40
	Day 2	0.43	0.43	1.19	1.29	0.76	1.04	1.00	0.98	1.12	1.31
	Day 3	0.43				1.01	0.76		0.62	0.73	0.79
	Day 4	0.86				0.63	0.43				0.84
	Day 5					0.42					0.53

\* See Key to tables

tion, as a subcutaneous injection at a single site. The average survival time was 12.6 days, but it should be observed that this was not an accurate reflection of the true picture, because the increased survival over the control Group I was primarily due to the prolonged survival of two animals, D-153 and D-174 (Table 2) where the initial bacterial flora in the duodenojejunal segment was zero. There is, however, evidence that a small degree of protection has been conferred by this single

subcutaneous dose of sulfathiazole which resulted in but a brief maintenance of a relatively low general systemic concentration of the drug. Twenty per cent of the animals lived more than 15 days. The changes in the composition of the blood were similar to those observed in Group I.

*Group III.*—One day preceding the usual operative procedures, these ten animals received 2.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, by subcutaneous injection at ten different sites. This procedure maintained a significant tissue level of sulfathiazole for approximately 10 days (Fig. 2). From the summarized data in Table 3 it was evident that less vomiting occurred post-operatively. This treatment conferred significant protection with 40 per cent of the animals living more than 15 days and an average survival period of 25.6 days for the entire group. Since the tissue was impregnated with sulfathiazole twenty-four hours before contamination of the peritoneal cavity, this group should represent the best results that can be expected from systemic treatment with sulfathiazole.

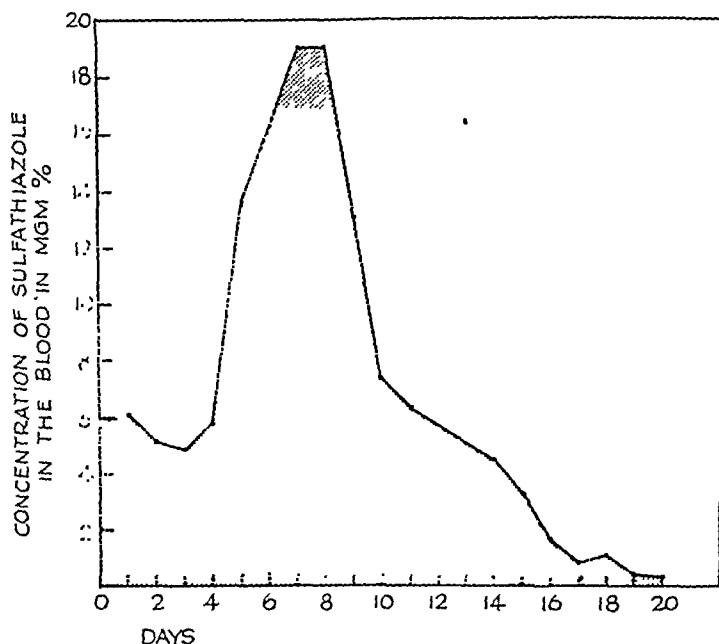


Fig. 2.—A characteristic chart of the concentration of sulfathiazole in the blood following the subcutaneous injection at ten different sites of a saline suspension of 2.5 Gm. of the drug per kilo of body weight.

*Group IV.*—At the time of the usual operation to form the duodeno-jejunal segment, 0.5 grams of sulfathiazole per kilo of body weight, suspended in normal salt solution, were injected into the general peritoneal cavity of ten animals. Sixty per cent of these animals survived more than 15 days and the average length of survival was 51.5 days. The concentration of sulfathiazole in the blood was appreciable for

the first 1 or 2 days indicating that the intraperitoneal concentration was high during this period. Those animals which survived more than a few days had only slight changes in the constituents of their blood. At autopsy there was no evidence of "caking" of the drug. The peritoneal cavity contained a moderate amount of clear sanguineous fluid. This fluid did not have a foul odor.

Table 3. Loop washed with 10 cc of physiologically normal salt solution. 2.5 gms of sulfathiazole per kilo of body weight suspended in normal salt solution + divided into 10 portions was injected subcutaneously at 10 different sites 1 day before duodenojejunal loop was made.

Animal	D-147	D-148	D-149	D-150	D-151	D-165	D-166	D-167	D-168	D-169
Days of Survival	70	2	2 1/2	70	1 1/2	4	3	36	2	65
Bacterial Flora Initial (a)	Count None	Average A.B	0 None	Average C.G	High C.G.I.J	High A.B.K	Low A.B.I.J	Low A.B.C	0 None	Average A.B.D
Bacterial Flora Final (b)	Count None	High A.B	High A.B		High C.G.I	High A.B.K	High A.B.C.I	High A.B.C	High A.C	Low A.B
Blood Chlorides Mgm %	Initial	408	400	398	402	411	395	389	406	390
	Max.	408	400	398	402	411	395	389	414	390
	Min.	347	316	352	342	386	344	362	392	367
N.P.N Mgm %	Initial	18.4	21.9	32.7	25.5	20.3	19.4	22.6	23.8	18.6
	Max.	30.6	33.3	32.7	31.8	21.8	34.6	29.8	24.4	26.4
	Min.	18.4	21.9	24.5	22.0	20.3	19.4	22.6	20.6	18.6
Plasma Protein %	Initial	5.50	5.10	5.08	5.23	4.65	5.00	4.83	5.20	5.44
	Max.	5.84	5.20	5.79	5.54	5.34	5.60	5.70	5.55	5.80
	Min.	5.14	5.10	4.49	4.92	4.65	5.00	4.83	4.96	5.44
Hemoglobin Gms/100 cc	Initial	10.45	12.52	18.18	18.20	16.40	19.63	14.92	21.64	22.81
	Max.	10.45	12.52	22.56	20.85	16.40	21.40	18.67	22.04	24.54
	Min.	12.29	12.12	16.50	18.20	16.17	19.63	14.92	14.36	22.81
Blood Sulfathiazole Concentration Mgm %	Day 1	4.83	4.50	6.80	10.58	4.38	7.64	5.42	6.21	8.62
	" 2	8.32	3.91	15.65	5.82	3.67	8.44	4.37	5.48	7.76
	" 3	10.04		8.96	6.42		9.36	7.73	7.27	
	" 4	12.80			5.19		8.60		9.36	
	" 5	14.13			4.02				10.16	

\*See Key to Tables

Group V.—At the time of operation on ten animals, 0.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, were injected into the open duodenojejunal loop. A large portion of this fluid naturally poured into the general peritoneal cavity immediately, thereby distributing the drug between the loop and the peritoneal cavity. One hundred per cent of these animals survived for more than 15 days for an average period of 43.1 days. At autopsy these animals

showed a rather dry, chronic peritonitis. The odor was slight. The open end of the duodenojejunal loop was usually walled off, although on occasion it was found entirely free in the peritoneal cavity. It was noteworthy that the blood concentration of sulfathiazole was maintained at a higher level for a longer period than in the case of Group IV.

*Table 4. Loop washed with 10cc of physiologically normal salt solution. 0.5 grams of sulfathiazole per kilo of body weight suspended in 20cc of normal salt solution and injected into the general peritoneal cavity as abdomen was closed.*

Animal	D-154	D-155	D-156	D-157	D-158	D-186	D-187	D-188	D-189	D-190
Days of Survival	107	137	34	2	2	100	26	3	4	95
Bacterial Flora	Count	Average	Low	Low	Average	Low	0	Average	High	High
	Identity	A.B.N*	ACGH	AC.R	A.B.K.L	A.I	None	A.B.C	ABCG	ABHR
Bacterial Flora	Count	Low	Low	High	High	High	0	High	High	High
	Identity	A	AC	A.B.C	A.B.L	A.B	None	A.C	A.B.CG	A.B.H
Blood Chlorides	Initial	395	402	392	398	406	399	412	400	408
	Max	410 <sup>5</sup>	418 <sup>20</sup>	416 <sup>20</sup>	398 <sup>8</sup>	406	414 <sup>2</sup>	420 <sup>2</sup>	400 <sup>2</sup>	408 <sup>2</sup>
	Min.	376 <sup>4</sup>	402 <sup>2</sup>	382 <sup>3</sup>	374 <sup>2</sup>	361 <sup>2</sup>	381 <sup>3</sup>	366 <sup>2</sup>	356 <sup>3</sup>	342 <sup>2</sup>
N P N	Initial	20.6	31.3	24.6	25.4	22.8	23.7	21.5	19.8	17.3
	Max	27.6 <sup>2</sup>	33.3 <sup>2</sup>	26.4 <sup>2</sup>	35.5 <sup>2</sup>	36.4 <sup>2</sup>	26.5 <sup>2</sup>	24.7 <sup>2</sup>	31.6 <sup>2</sup>	41.6 <sup>2</sup>
	Min.	19.4 <sup>2</sup>	27.8 <sup>2</sup>	23.8 <sup>2</sup>	25.4 <sup>2</sup>	22.8 <sup>2</sup>	21.4 <sup>2</sup>	20.7 <sup>2</sup>	19.8 <sup>2</sup>	17.3 <sup>2</sup>
Plasma Protein %	Initial	4.35	5.75	5.23	5.97	5.48	5.85	5.10	4.93	5.60
	Max.	5.10 <sup>2</sup>	6.01 <sup>2</sup>	5.60 <sup>2</sup>	5.97 <sup>2</sup>	5.68 <sup>2</sup>	6.20 <sup>2</sup>	5.72 <sup>2</sup>	5.40 <sup>2</sup>	5.60 <sup>2</sup>
	Min.	4.20 <sup>2</sup>	5.65 <sup>2</sup>	5.14 <sup>2</sup>	4.60 <sup>2</sup>	5.48 <sup>2</sup>	5.40 <sup>2</sup>	5.00 <sup>2</sup>	4.93 <sup>2</sup>	4.90 <sup>2</sup>
Hemoglobin	Initial	17.48	13.59	15.94	15.90	16.74	18.03	19.24	19.26	18.27
	Max.	18.35 <sup>2</sup>	15.92 <sup>2</sup>	17.36 <sup>2</sup>	20.40 <sup>2</sup>	19.63 <sup>2</sup>	22.18 <sup>2</sup>	21.18 <sup>2</sup>	21.43 <sup>2</sup>	26.07 <sup>2</sup>
	Min.	16.22 <sup>2</sup>	12.18 <sup>2</sup>	13.32 <sup>2</sup>	15.90 <sup>2</sup>	16.74 <sup>2</sup>	16.73 <sup>2</sup>	18.60 <sup>2</sup>	19.26 <sup>2</sup>	18.27 <sup>2</sup>
Sulfathiazole Concentration	Day 1	4.18	6.24	5.80	5.26	4.78	3.51	4.82	6.21	5.42
	Day 2	2.06	5.36	6.10	4.18	2.26	3.04	3.67	3.18	4.82
	Day 3	0.98	1.29	2.42			1.62	1.96		2.76
	Day 4	0.46	0.76	1.20			0.90	0.53		0.62
	Day 5	0.23	0.31	0.41			0.32	0.71		0.30

\* See Key to Tables

Group VI.—In ten animals, 0.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, was injected into the open duodenojejunal loop as well as 0.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, injected subcutaneously immediately after operation and daily thereafter for 5 days. All of these animals lived longer than 15 days for a survival period of 44.6 days. The blood sulfathiazole was maintained at a significant level for several days although not so high or for as long a period of time as in the case of Group 3. At autopsy a chronic, dry peritonitis was encountered; little odor was present.

# DISCUSSION

The results of these experiments to determine the differential advantage of the administration of sulfathiazole by different routes in the treatment of this experimentally produced peritonitis seem quite definite. The experimental preparation employed in this study for the production of a peritonitis caused a 100 per cent mortality for the control animal and was not so severe that it did not respond in a differential manner to the varied forms of therapy used.

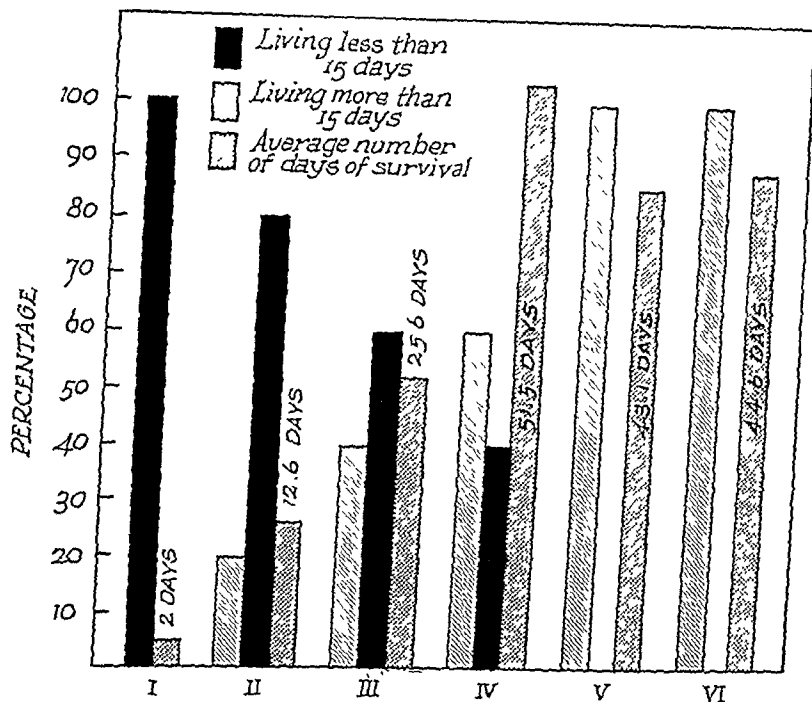


Fig. 3.—Plotting survival data of six groups of ten dogs each, each animal being operated upon to form an isolated, open duodenojejunum, as follows: Group I: Segment formed but not treated with . . . . . group of animals to serve as controls. Group II: 0.5 Gm. of . . . . . of body weight injected subcutaneously as a suspension at a site . . . . . following operation. Group III: 2.5 Gm. of sulfathiazole per kilo of body weight injected subcutaneously as a suspension in ten different sites on day preceding operation. Group IV: 0.5 Gm. of sulfathiazole per kilo of body weight injected into the peritoneal cavity as a suspension at time of operation. Group V: 0.5 Gm. of sulfathiazole per kilo of body weight injected into the open duodenojejunal segment as a suspension at time of operation. Group VI: 0.5 Gm. of sulfathiazole per kilo of body weight injected into the open duodenojejunal segment and an equal quantity of the drug injected subcutaneously as a suspension in a single site at time of operation and for 1 successive days thereafter.

The data obtained in these experiments have been summarized in the tables and are included because of the wide difference between the bacterial flora present in individual animals and these facts make it imperative that exact information be available in an experiment including such small numbers of animals. Reference to the tables will show that the bacterial flora in the duodenum and first part of the jejunum may not be small, as is frequently assumed. The number of organisms may be as



great as are encountered in the large bowel, therefore, to draw any conclusions from an individual experiment, this information is essential and must be recorded.

The duodenojejunal loop, open at one end, serves as a constant source of infection. The deposition of sulfathiazole into this loop serves a double purpose. The drug alters and probably attenuates the contained bacterial flora and acts as a reservoir of drug which is subsequently

Table 5 - Loop washed with 10 cc of physiologically normal salt solution 0.5 grams of sulfathiazole per kilo of body weight suspended in 20 cc of normal salt solution injected into the open duodenojejunal loop

Animal	D-141	D-142	D-143	D-144	D-145	D-160	D-161	D-162	D-163	D-164		
Days of Survival	35	68	50	30	45	75	26	32	47	53		
Bacterial Flora	Initial (a)	Count	Average	0	Low	High	High	Low	High	High	Low	Average
	Final (b)	Identity	A.B. D.J.R.	None	C.E	B.L	A.B.H K.M.R	AC.E	ABJL	ABDR	ABC	AEL
Blood Chlorides Mm <sup>3</sup>	Initial	Count	Average		Average	High	High	Low	High	High	Average	High
	Final	Identity	C.D		ACJK	ABCI	ABC	H	ABC	AB	ABC	A.L
N.P.N. Mm <sup>3</sup> %	Initial	403	400	407	392	396	405	420	380	410	396	
	Max	406	411	411	410	403	416	442	396	422	406	
	Min	356	379	378	299	329	390	330	321	376	385	
Plasma Protein	Initial	20.0	21.1	27.7	25.2	29.3	26.1	24.5	22.6	23.4	26.8	
	Max	25.9	29.7	27.7	33.1	29.3	28.9	30.6	31.6	27.5	28.7	
	Min	18.5	20.5	22.1	17.7	17.5	22.7	18.6	17.3	20.7	22.4	
Hemoglobin Gms/100 cc	Initial	4.35	5.23	5.48	5.10	5.60	4.80	5.32	4.68	5.52	4.76	
	Max	5.20	5.24	5.54	5.55	6.51	5.20	5.70	5.62	5.71	4.92	
	Min	3.89	4.23	4.77	4.71	4.29	4.52	4.30	4.28	5.21	4.30	
Blood Sulfathiazole Concentration Mm <sup>3</sup>	Initial	13.95	17.68	15.09	17.23	18.30	16.87	19.62	14.63	15.74	20.46	
	Max	18.40	20.40	15.58	17.70	21.60	17.23	22.34	18.76	16.36	22.16	
	Min	10.22	12.51	10.02	15.85	10.30	12.60	10.16	12.42	14.71	19.87	
Blood Sulfathiazole Concentration Mm <sup>3</sup>	Day 1	6.42	3.79	6.42	1.29	3.21	5.31	4.32	5.80	3.92	6.20	
	" 2	7.93	2.53	5.94	2.64	2.18	5.11	3.26	3.92	4.10	5.50	
	" 3	0.86	1.51	2.30	4.14	3.09	3.26	2.72	2.14	2.05	3.64	
	" 4	0.86	0.43	2.18	1.73	1.73	1.60	1.40	1.70	1.64	2.82	
	" 5	0.54	1.29	1.73	1.40	2.64	1.10	0.92	1.02	0.52	1.31	

\*See Key to Tables

forced into the general peritoneal cavity to replace the drug absorbed by the peritoneal surfaces as indicated by the relative blood levels of sulfathiazole in Groups IV and V.

The survival of the animals in Groups IV, V, and VI, and especially in Groups V and VI, as contrasted with the survival rates in Groups II and III, demonstrated the importance of, and the therapeutic value of, main-

taining a high local concentration of sulfathiazole in the area of infection. These observations logically suggest a possible value of repeated injections of a suspension of sulfathiazole into the peritoneal cavity in the presence of a generalized peritonitis, without localization, to maintain a sustained high local concentration of the drug over an extended period.

*Table 6 - Loop washed with 10cc of physiologically normal salt solution 0.5 grams of sulfathiazole per kilo of body weight suspended in 20 cc of  $\frac{1}{2}$ % injected into the open duodenojejunal loop 0.5 gms of sulfathiazole per kilo of body weight suspended in 20 cc of  $\frac{1}{2}$ % deposited*

Animal	D-120	D-122	D-124	D-125	D-126	D-127	D-129	D-130	D-137	D-139		
Days of Survival	60	22	16	60	17	71	50	50	40	60		
Bacterial Flora	Initial	Count Identity	Low <sup>AH</sup> <sub>I,K,R</sub>	High A,B,P	High A,I,M	Low N	Low A,B,C	Average <sup>AH</sup> <sub>K,L,Q</sub>	Average A,B,G	Low ABC	High A,B,N	Average A,M
	Final	Count Identity	High A,C,P	High A,B,P	High A,M	Low A,C,H	High A,B,C,I	Low A,H,K,Q	Average C,H	High A,G	High B,F	High C
Blood Chlorides Mgm %	Initial	405	394	392	398	416	404	395	402	405	407	
	Max	419 <sup>a</sup>	413 <sup>a</sup>	392 <sup>a</sup>	436 <sup>a</sup>	416 <sup>a</sup>	436 <sup>a</sup>	409 <sup>a</sup>	421 <sup>a</sup>	430 <sup>a</sup>	423 <sup>a</sup>	
	Min	354 <sup>a</sup>	322 <sup>a</sup>	220 <sup>a</sup>	300 <sup>a</sup>	356 <sup>a</sup>	324 <sup>a</sup>	271 <sup>a</sup>	300 <sup>a</sup>	328 <sup>a</sup>	371 <sup>a</sup>	
N.P.N. Mgm %	Initial	23.7	27.5	25.5	24.0	26.1	29.8	19.3	19.3	25.4	24.7	
	Max	39.5 <sup>a</sup>	30.6 <sup>a</sup>	42.1 <sup>a</sup>	39.6 <sup>a</sup>	27.1 <sup>a</sup>	66.2 <sup>a</sup>	71.3 <sup>a</sup>	29.4 <sup>a</sup>	29.4 <sup>a</sup>	37.2 <sup>a</sup>	
	Min	18.7 <sup>a</sup>	17.1 <sup>a</sup>	21.7 <sup>a</sup>	22.3 <sup>a</sup>	22.7 <sup>a</sup>	20.3 <sup>a</sup>	18.4 <sup>a</sup>	19.3 <sup>a</sup>	15.1 <sup>a</sup>	18.7 <sup>a</sup>	
Plasma Protein %	Initial	5.84	6.26	4.95	6.27	6.41	5.31	5.09	6.59	6.29	4.85	
	Max	6.26 <sup>a</sup>	7.26 <sup>a</sup>	5.29 <sup>a</sup>	7.10 <sup>a</sup>	6.41 <sup>a</sup>	6.01 <sup>a</sup>	6.33 <sup>a</sup>	7.14 <sup>a</sup>	6.29 <sup>a</sup>	5.55 <sup>a</sup>	
	Min.	4.64 <sup>a</sup>	5.43 <sup>a</sup>	4.23 <sup>a</sup>	4.30 <sup>a</sup>	4.67 <sup>a</sup>	4.54 <sup>a</sup>	4.52 <sup>a</sup>	5.30 <sup>a</sup>	4.86 <sup>a</sup>	4.41 <sup>a</sup>	
Hemoglobin Gms/100 cc	Initial	16.52	15.92	20.17	18.30	18.42	14.65	15.03	12.79	19.18	15.92	
	Max	22.02 <sup>a</sup>	21.60 <sup>a</sup>	22.65 <sup>a</sup>	20.84 <sup>a</sup>	19.89 <sup>a</sup>	15.84 <sup>a</sup>	15.83 <sup>a</sup>	16.83 <sup>a</sup>	21.58 <sup>a</sup>	17.60 <sup>a</sup>	
	Min	11.39 <sup>a</sup>	8.76 <sup>a</sup>	17.2 <sup>a</sup>	8.11 <sup>a</sup>	10.71 <sup>a</sup>	5.46 <sup>a</sup>	8.58 <sup>a</sup>	6.65 <sup>a</sup>	12.10 <sup>a</sup>	7.97 <sup>a</sup>	
Blood Sulfathiazole Concentration Mgm %	Day 1	11.08	3.91	4.26	6.42	5.31	3.44	2.64	4.02	2.75	5.07	
	" 2	9.37	3.55	2.64	5.07	6.67	3.97	3.55	2.41	4.61	2.18	
	" 3	1.95	2.64	2.86	3.09	1.73	2.21	2.30	2.86	7.30	1.62	
	" 4	1.29	2.18	1.51	1.73	1.84	2.96	0.86	1.73	3.09	5.44	
	" 5	2.53	4.02	1.95	1.73	1.29	1.08	1.73	1.29	3.09	1.40	

\* See Key to Tables

Groups V and VI cannot be compared directly with the preceding groups because the drug had been placed in the loop and probably served to attenuate the organisms, inhibit their growth, or prevent the formation of greater quantities of sulfonamide inhibitors by the metabolic action of the bacteria in the loop, so that these elements contaminated the general abdominal cavity to a lesser degree.<sup>11</sup> These ex-

periments should serve, however, to demonstrate the beneficial effect of a high local concentration of the drug in controlling infection.

While Groups V and VI fail to show any difference in the effectiveness of treatment because 100 per cent survival resulted in both experiments, Stafford (1942),<sup>12</sup> in contrasting two series of acute appendicitis with peritonitis and abscesses, showed that the incidence of secondary complications were decreased following the use of sulfathiazole by mouth or intravenously. From these observations it would appear that the sulfonamides should be given by both the intraperitoneal and other routes to establish a high local concentration and maintain the desired systemic drug level in the treatment of peritonitis.

A suspension of sulfathiazole in contradistinction to the dry powdered form of the drug is apparently more uniformly distributed and shows little tendency to "cake" or act as an irritating foreign body and may permit the use of this more powerful bacteriostatic agent instead of the more toxic and less active sulfanilamide, which has been favored for intraperitoneal insufflation because of its more suitable physical properties.

The value of using sulfathiazole locally in the peritoneal cavity in conjunction with succinylsulfathiazole, when employed to alter the bacterial flora of the intestinal tract<sup>13-16</sup> prior to elective surgery on the large bowel, becomes evident and is advocated as an additional adjuvant to modern surgery of the colon whenever soiling occurs during operation.

#### SUMMARY

1. A method for maintaining a therapeutic concentration of sulfathiazole in experimental animals over a long period is described.

2. A simple preparation for the production of a generalized peritonitis well suited to the study of the value of chemotherapeutic agents is presented.

3. A study of the bacterial flora of the duodenum and upper jejunum is reported.

4. The value of sulfathiazole when applied locally to the peritoneal cavity is assessed as compared to its usefulness when administered so as to maintain a relatively high general tissue concentration.

5. The suggestions are made that a suspension of sulfathiazole may be more suitable than the dry powder for intraperitoneal administration and that repeated intraperitoneal injections may be advisable in generalized peritonitis.

6. The results of this study indicate that the intraperitoneal administration of sulfathiazole should be fortified by maintaining a high systemic concentration of the drug by other therapeutic routes when necessary.

7. The combined use of succinylsulfathiazole and sulfathiazole as an adjuvant to surgery of the large bowel is advocated.

taining a high local concentration of sulfathiazole in the area of infection. These observations logically suggest a possible value of repeated injections of a suspension of sulfathiazole into the peritoneal cavity in the presence of a generalized peritonitis, without localization, to maintain a sustained high local concentration of the drug over an extended period.

*Table 6. - Loop washed with 10 cc of physiologically normal salt solution 0.5 grams of sulfathiazole per kilo of body weight suspended in 20 cc of  $\frac{1}{2}$  injected into the open duodenojejunal loop 0.5 gms. of sulfathiazole per kilo of body weight suspended in 20 cc of  $\frac{1}{2}$  deposited.*

Animal	D-120	D-122	D-124	D-125	D-126	D-127	D-129	D-130	D-137	D-139
Days of Survival	60	22	16	60	17	71	50	50	40	60
Bacterial Flora	Count	Low	High	High	Low	Low	Average	Average	Low	High
	Identity	A.H. I.K.R.	A.B.P.	A.I.M.	N	A.B.C.	A.B.H. K.L.Q.	A.B.G.	A.B.C.	A.B.N.
Bacterial Flora	Count	High	High	High	Low	High	Low	Average	High	High
	Identity	A.C.P.	A.B.P.	A.M.	A.C.H.	A.B.C.	A.H.K.Q.	C.H.	A.G.	B.F.
Blood Chlorides Mgm %	Initial	405	394	392	398	416	404	395	402	405
	Max.	419 <sup>0</sup>	413 <sup>0</sup>	392 <sup>0</sup>	436 <sup>0</sup>	416 <sup>0</sup>	436 <sup>0</sup>	409 <sup>0</sup>	421 <sup>0</sup>	430 <sup>0</sup>
	Min.	354 <sup>2</sup>	322 <sup>2</sup>	220 <sup>5</sup>	300 <sup>5</sup>	356 <sup>5</sup>	324 <sup>4</sup>	271 <sup>21</sup>	300 <sup>0</sup>	328 <sup>1</sup>
N.P.N Mgm %	Initial	23.7	27.5	25.5	24.0	26.1	29.8	19.3	19.3	25.4
	Max	39.5 <sup>5</sup>	30.8 <sup>0</sup>	42.1 <sup>1</sup>	39.0 <sup>5</sup>	27.1 <sup>8</sup>	66.2 <sup>2</sup>	71.3 <sup>21</sup>	29.4 <sup>5</sup>	29.4 <sup>5</sup>
	Min	18.7 <sup>1</sup>	17.1 <sup>1</sup>	21.7 <sup>2</sup>	22.3 <sup>3</sup>	22.7 <sup>1</sup>	20.3 <sup>3</sup>	18.4 <sup>1</sup>	19.3 <sup>1</sup>	15.1 <sup>1</sup>
Plasma Protein %	Initial	5.84	6.26	4.95	6.27	6.41	5.31	5.09	6.59	6.29
	Max	6.26 <sup>0</sup>	7.20 <sup>0</sup>	5.29 <sup>0</sup>	7.10 <sup>0</sup>	6.41 <sup>0</sup>	6.01 <sup>0</sup>	6.33 <sup>0</sup>	7.14 <sup>0</sup>	6.20 <sup>0</sup>
	Min.	4.64 <sup>0</sup>	5.43 <sup>0</sup>	4.23 <sup>0</sup>	4.30 <sup>0</sup>	4.67 <sup>0</sup>	4.54 <sup>0</sup>	4.52 <sup>0</sup>	5.30 <sup>0</sup>	4.86 <sup>0</sup>
Hemoglobin Gms/100 cc	Initial	16.52	15.92	20.17	18.30	18.42	14.65	15.03	12.79	19.18
	Max.	22.02 <sup>0</sup>	21.60 <sup>0</sup>	22.65 <sup>0</sup>	20.84 <sup>0</sup>	19.80 <sup>0</sup>	15.84 <sup>0</sup>	15.83 <sup>0</sup>	16.83 <sup>0</sup>	21.58 <sup>0</sup>
	Min.	11.39 <sup>0</sup>	8.76 <sup>0</sup>	17.2 <sup>0</sup>	8.11 <sup>0</sup>	10.71 <sup>0</sup>	5.46 <sup>0</sup>	8.58 <sup>0</sup>	6.65 <sup>0</sup>	12.10 <sup>0</sup>
Blood Sulfathiazole Concentration Mgm %	Day 1	11.08	3.91	4.26	6.42	5.31	3.44	2.64	4.02	2.75
	" 2	9.37	3.55	2.64	5.07	6.67	3.97	3.55	2.41	4.61
	" 3	1.95	2.64	2.86	3.09	1.73	2.21	2.30	2.86	7.30
	" 4	1.29	2.18	1.51	1.73	1.84	2.96	0.86	1.73	3.09
	" 5	2.53	4.02	1.95	1.73	1.29	1.08	1.73	1.29	3.09

\* See Key to Tables

Groups V and VI cannot be compared directly with the preceding groups because the drug had been placed in the loop and probably served to attenuate the organisms, inhibit their growth, or prevent the formation of greater quantities of sulfonamide inhibitors by the metabolic action of the bacteria in the loop, so that these elements contaminated the general abdominal cavity to a lesser degree.<sup>11</sup> These ex-

# ANOXIA AND ANESTHESIA IN INTRATHORACIC OPERATIONS

## A CLINICAL STUDY\*

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ANOXIA, a diminution in the normal amount of oxygen in the various tissues and organs of the body, was the most important single factor which delayed the development of surgical operations for lesions within the thoracic cavity. Since the heart and lungs are chiefly responsible for supplying oxygen to the tissues, alteration of their function by opening the chest led to serious consequences. The ill effects of an open pneumothorax on cardiorespiratory function were demonstrated as long ago as the sixteenth century by the anatomist Vesalius<sup>1</sup> to his students. He also demonstrated to them, by the use of a reed in the trachea, how these deleterious reactions could be prevented or overcome by repeated inflation of the lung. Before the establishment of aseptic surgical principles by Lister<sup>2</sup> and the development of diagnostic methods (Roentgen,<sup>3</sup> and Killian<sup>4</sup>), the experimental findings of Vesalius could not be applied in clinical practice until within the last two or three decades.

The importance of anoxia occurring during surgical procedures in general has recently received more attention (McClure and associates,<sup>5</sup> and Schnedorf and associates<sup>6</sup>). The chief investigation has been directed toward the anesthetic agent used and the amount of available oxygen during the operative procedure.

The anesthetic agent of choice and the method of administration for intrathoracic operations continue to be controversial problems. Some anesthetists or surgeons prefer cyclopropane,<sup>7, 8</sup> while others prefer ether,<sup>9</sup> ethylene,<sup>10</sup> or spinal anesthesia.<sup>11</sup> Opinions are also divided as to whether an intratracheal catheter is advisable and, if so, in what types of patients or diagnostic conditions.<sup>7, 9, 12-15</sup> Most surgeons at the present time are agreed that the anesthetic mixture should be administered under mild positive pressure when the pleural cavity is opened.

Since alteration of cardiorespiratory function is apt to occur when the pleural cavity is opened, the role of anoxia assumes even greater importance in intrathoracic operations.

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TABLE I

## CONTRIBUTORY FACTORS IN THE PRODUCTION OF ANOXIA DURING INTRATHORACIC OPERATIONS

DECREASED EFFICIENCY OF THE RESPIRATORY EFFORT	
Open chest	
1. Loss of negative intrapleural pressure	
2. Movement of mediastinum	
3. Inefficient muscular activity	
Position on table	
1. Interferes with chest motion	
2. Good lung dependent	
Diaphragmatic paralysis	
DECREASED VENTILATION OF LUNG	
Obstruction of airway by secretions	
Collapse of lung	
Removal of lung	
Disease of lung	
1. Inflammatory	
2. Neoplastic	
3. Emphysema—asthma	
4. Fibrosis	
DECREASED CARDIAC OUTPUT	
Obstruction of veins and auricles by retractors and lap pads	
Increased intrabronchial pressure	
Abnormal cardiac action	
1. Tachycardia	
2. Flutter	
3. Fibrillation	
ALTERATION OF O <sub>2</sub> TRANSPORT MEDIA	
Anemia	
Blood loss during and following operation	
Arteriovenous shunt (collapsed lung)	

of the dependent side. Following the operation the air passages are thoroughly cleared by bronchoscopic aspiration.

Attention must be given to the careful use of large, moist gauze packs and retractors since little pressure is needed to obstruct the blood flow through large veins, or to compress the auricles, thus leading to decreased cardiac output and lowering of systemic blood pressure.

Many patients requiring operations within the chest have some degree of anemia when first seen. Since normal cardiac action and sufficient respiratory reserve with adequate gas exchange in the lungs will not compensate for lack of hemoglobin, treatment of this anemia with blood transfusion is indicated. In addition to the administration of blood before surgery, a continuous transfusion of 500 to 1,000 c.c. (or at times more) during operation is almost routine at our clinic. This is usually no more than replacement of blood lost during and immediately following the operation and goes far in the prevention of anoxia as well as shortening convalescence. This blood is given before any evidence of shock appears.

In a previously reported series of intrathoracic operations,<sup>10</sup> no blood transfusions were given in the operating room and no symptoms of shock were observed. However, postoperative hematocrit studies re-

# CONTRIBUTORY FACTORS IN THE PRODUCTION OF ANOXIA IN INTRATHORACIC OPERATIONS

In the transportation of oxygen from an inhaled gas to various tissues of the body, certain factors especially related to intrathoracic operations may play a major part in the development of anoxia (see Table I).

When the pleural cavity is opened there is an immediate reduction of negative pressure on the opposite side. With each inspiratory effort the mediastinum is pulled toward the unoperated side, thus further reducing the effectiveness of the respiratory effort. The hindrance of action of the respiratory muscles may be considerable, due to the use of self-retaining rib spreading retractors and the side position with slight Trendelenburg on the operating table, particularly in older, obese, or debilitated patients. Thus, it is obvious that decreased efficiency of the respiratory effort can materially reduce the amount of gas exchange within the lungs and lead to the development of anoxia.

Ventilation of the lung may be further decreased by obstruction of the air passages with mucus, pus, or blood. This is more likely to occur in patients with suppurative diseases of the lung. The vital capacity may be already considerably reduced due to inflammatory, neoplastic, or degenerative changes in the lung, and will be further reduced by collapse of the lung when the pleura is opened.

It is a well-known fact that the respiratory reserve of a normal man or animal is high, several times the amount of function ordinarily needed (Graham,<sup>16</sup> Phillips and co-workers,<sup>17</sup> and Rasmussen and co-workers<sup>18</sup>). It has also been repeatedly demonstrated that operations in the open thorax may be made under spinal anesthesia with little or no positive pressure applied to the tracheobronchial tree (Edwards,<sup>11</sup> and Magill<sup>19</sup>). However, since many patients needing intrathoracic operations already have a reduction in the respiratory reserve, most surgeons have agreed that a mild increase in the intrabronchial pressure is advisable during these procedures. This pressure should not be so high as to obstruct the flow of blood through the lungs, thus producing decreased cardiac output with a resultant drop in systemic blood pressure, but only enough (4 to 8 mm. Hg) to stabilize the mediastinum and keep the lungs partly inflated.

Obstruction of the air passages may be obviated by preoperative removal of secretions and pus by postural or bronchoscopic drainage. During operation, a slight lowering of the head of the table (20 to 30 degrees) will aid in the removal of mucus and pus by gravity drainage. In patients having a productive cough, bronchoscopic aspiration in the operating room following surgery is the routine in this clinic. In cases of bilateral bronchiectasis, Blades and Graham<sup>20</sup> have advocated elevation of the head of the table during operation to aid in "internal drainage" of secretions from the lobes to be removed into the lower lobe



need for deep anesthesia. At one time ethylene plus oxygen alone was used and the percentage of ethylene was increased when deeper anesthesia was needed. It was found, however, that in patients with pulmonary suppurative disease this was at times unsatisfactory because of symptoms of anoxia and we have since added ether and more oxygen, thereby obtaining deeper anesthesia and better oxygenation. During the closure of the chest wall in this latter group of cases, nitrous oxide-oxygen is substituted and explosive mixtures in machines are removed from the room. This permits the use of bronchoscopic aspiration for the thorough clearing of the air passages of pus and secretions at the end of operation.

The anesthetic agent in this series of operations has been administered under slight positive pressure (4 to 8 mm. Hg) using the semiopen system with a snug-fitting face mask. An intratracheal catheter has only occasionally been employed and this was in patients with bilateral bronchiectasis who were raising a large amount of sputum. It has not

TABLE II

DIAGNOSIS, NUMBER AND CAUSE OF POSTOPERATIVE DEATHS OCCURRING IN 51 INTRA-THORACIC OPERATIONS (45 PATIENTS)

DIAGNOSIS	NO. OF PATIENTS	NO. OF DEATHS	TIME OF DEATH	CAUSE OF DEATH
Carcinoma of lung	9	1 exploratory thoracotomy 2 pneumonectomy	3 days P.O. 2 weeks P.O. 2 weeks P.O.	Pulmonary edema Anuria Pericarditis
Bronchiectasis	10*	1 bilobectomy (bilateral bronchiectasis)	4 days P.O.	Pneumonia
Carcinoma of esophagus or stomach (Benign stricture, 1)	12	2 carcinoma of cardia resection	8 days P.O. 1 day P.O.	Massive empyema Cardiac failure
Mediastinal tumor or cyst	3	None	-	-
Malignant hypertension (14 operations)	8	None	-	-
Constrictive pericarditis	2	None	-	-
Patent ductus arteriosus	1	None	-	-

\*One case of infected cyst of the lung and one of chronic infection of the lung are included in this group.

been found necessary in other patients, and the elimination of irritation of the tracheal mucous membrane from the presence of a foreign object for a period of time, we feel, has definitely improved the convalescence period. At the termination of the operation, complete obliteration of the pleural space through re-expansion of the lung was obtained by aspiration of the residual air through a pezzet catheter drain rather than by distention of the lung through the use of a high intrabronchial pressure. This prevents the driving of infectious material out into the periphery of the lung as well as overdistention and damage of the lung

vealed that a moderate to severe grade of anemia was present without evidence of circulatory failure.

Since the reduction in arterial blood oxygen may have a severe detrimental effect on the patient both during and following the operation we have thought it worth while to investigate its frequency and severity in our patients. The continual controversy regarding both the most desirable anesthetic agent and the proper method of its administration in intrathoracic operations has been an added stimulus for this inquiry. To this end both clinical and experimental studies have been conducted. A preliminary report of the clinical work appears elsewhere,<sup>21</sup> and a complete report of the experimental investigation will be published in a separate communication.<sup>22</sup>

In order to determine the maximum influence of the operative procedure as well as the anesthesia on arterial blood oxygen, specimens of arterial blood were taken near the end of the operation just before closing the pleural cavity. These were obtained from the radial or brachial artery using a mercury tenonometer. This sample was then compared with samples of arterial blood obtained during the twenty-four hours prior to operation, and again four to fourteen days following operation. Erythrocyte count, hematocrit, hemoglobin, and oxygen content determinations were made on these specimens of arterial blood. The oxygen content was determined according to the Van Slyke-Neill<sup>23</sup> manometric method and the value recorded in volume per cent. The anesthetic record of each patient showed the per cent of oxygen in the anesthetic mixture when the sample of arterial blood was obtained as well as the average percentage of oxygen used during the entire operation. This was then compared to the oxygen in the three samples of arterial blood. All blood oxygen determinations were made in duplicate.

In the preparation of our patients for intrathoracic operations, attention has been given to blood transfusion in patients with anemia, and to postural or bronchoscopic drainage in patients with suppurative disease of the lung. In patients with esophageal obstruction due to carcinoma of the esophagus or cardia, water and electrolyte losses are replaced and the nutritional state improved before undertaking the operative procedure. During this study most of our patients received morphine (0.010 to 0.015 Gm. [hypodermic]) and calcium nembutal (0.18 to 0.27 Gm. in 50 c.c. of water per rectum) one and one-half hours before anesthesia. The dosage varied according to the age, size, sex, and general condition of the patient. In patients with hypertension, avertin (approximately 70 to 80 mg./kilogram) was sometimes employed for basal anesthesia, particularly when  $N_2O-O_2$  anesthesia was to be used because of the presence of electrical devices.

The anesthetic mixture used for these operations for the most part was ethylene plus oxygen or ethylene-oxygen plus ether. The anesthetic mixture depended upon the degree of resistance of the patient and the

of the entire thoracic sympathetic chain and usually included the first lumbar ganglion. The operating time for this group averaged two hours.

With the exception of patients Nos. 2, 5, and 6 the condition of the preoperative blood was within normal limits. In Nos. 5 and 6 the hypertension was so great that a transfusion for correcting a marked anemia was thought to be hazardous.

Throughout this group the state of the arterial sample taken at operation showed little change from that of the preoperative specimen. The oxygen values of some patients were higher during operation, while others were slightly better before operation. The postoperative samples will be discussed later. With the exception of patients Nos. 4, 5, and 6 no anoxia was observed; however, Nos. 5 and 6 were actually improved in comparison to their preoperative state. In spite of the degree of anoxia present in this patient (A. P.) no cyanosis was observed because of the degree of anemia present.

The percentage of oxygen used in the anesthetic mixtures varied from 12 to 40. Equally satisfactory blood oxygenation was obtained with the four different anesthetic mixtures used.

*Carcinoma of the Esophagus or Cardia* (Table V).—Of the twelve operations in this group, six were resections and six were only explorations. Due to the nature of the condition all operations lasted at least two hours and some resections required four hours. The majority of these patients required opening of the diaphragm in addition to the thoracotomy wound; and in some either a gastrostomy, gastroesophagostomy, or a cervical esophagostomy was made. As a group they were considered a better operative risk than those in Table IV, most patients being classified as good or fair. There were no anesthetic deaths. With the exception of the first patient the preoperative blood samples showed relatively normal values and remained the same during the operation. Ten of the twelve operations were made under an anesthetic mixture of ethylene plus 13 to 48 per cent oxygen. The preanesthetic medication produced marked depression in patient No. 10, thus demanding a higher percentage of oxygen in the anesthetic mixture. No cyanosis was observed in this group of patients and blood oxygenation was satisfactory. The postoperative values were often lower than the preoperative and operative levels and will be discussed later.

*Carcinoma of the Lung* (Table VI).—Nine patients are included in this group, in four of whom only an exploratory thoracotomy was made. This group as a whole were fair-risk patients, with the exception of patients Nos. 2 and 4. The operations lasted for an average of two and one-half hours. In patients Nos. 1, 2, 6, and 9 an exploration only was made. However, before operability could be determined, a considerable amount of dissection was necessary in both patients Nos. 2 and 9.

In patient No. 2 exploration was probably inadvisable due to his extremely poor condition. Cyanosis was not present either before or

tissue. The pathologic lesions included in this study as well as the post-operative deaths are presented in Table II. A variety of operations were made on these patients, as shown in Table III.

TABLE III  
TYPE OF OPERATION

	NUMBER	DEATHS
1. Exploratory thoracotomy for:		
Carcinoma of lung	6	1
Carcinoma of esophagus or cardia	6	0
2. Pneumonectomy	3	2
3. Lobectomy or bilobectomy	10	1
4. Extirpation of mediastinal tumor or cyst	3	0
5. Partial resection of thoracic esophagus or esophagus and stomach	6	2
6. Thoracic paravertebral sympathectomy	11	0
7. Pericardectomy (partial)	2	0
8. Ligation of patent ductus arteriosus with associated subacute bacterial endarteritis	1	0

None of the deaths in this group were related directly or indirectly to the anesthesia. One postpneumonectomy death was due to anuria following the administration of sulfathiazole in the usual amount. The death following exploration for carcinoma of the lung was due to cardiac failure. The operation should not have been made since the arterial blood oxygen was only 11.64 volumes per cent before operation. One child with bilateral bronchiectasis died of pneumonia four days following a bilobectomy. This was believed to be due to the poor general condition and massive and prolonged lung disease. Cardiac failure was responsible for one death twenty-four hours following an esophageal resection for carcinoma, while a second death was due to leakage of the anastomosis with massive empyema following the resection of 80 per cent of the stomach and lower esophagus. Most of these deaths occurred in poor-risk patients.

#### RESULTS

The results are presented in Tables IV, V, VI, VII, and VIII. The data are arranged to show values of arterial blood samples obtained before, during, and following the operative procedure and are grouped according to the anesthetic agents employed. The anesthetic risks are given in the second column, i.e., E, excellent; G, good; F, fair, and P, poor. This risk was determined on the basis of the patient's general condition, degree of toxicity, and debilitation, in addition to the local disease.

*Thoracic Sympathectomy for Essential Hypertension* (Table IV).—Fourteen operations made on eight patients are included in this group. Although the majority of these patients were considered only fair or poor operative risks, judged by cardiorenal and vascular changes, there was no operative mortality. Each operation consisted of two transpleural approaches (through the third and tenth rib-beds) for removal

TABLE V  
STATE OF ARTERIAL BLOOD BEFORE, DURING, AND FOLLOWING TRANSPLEURAL OPERATION FOR CARCINOMA OF THE ESOPHAGUS OR CARDIA  
IN 12 PATIENTS

PATIENT	PREOPERATIVE					DURING OPERATION					POSTOPERATIVE						
	CONDI- TION	HR. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	O.T. (HR.)	HR. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	O <sub>2</sub> GIVEN		HR. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	
											A	B					
Ethylene + O <sub>2</sub> Anesthesia																	
1. A. M.	P	76	4.05	34	12.57	3 3/4	80	4.26	35	13.81	15	15	70	4.21	35.5	14.03	
2. M. W.*	G	86	5.0	35	16.11	2	84	4.9	37	15.54	17	16	84	4.6	35	14.88	
3. N. D.*	G	88	4.8	34	18.23	2 1/2	84	4.7	35	16.37	16	16	100	4.1	35	18.86	
4. S. C.*	G	90	4.8	40	19.40	2 3/4	94	4.7	40	17.35	15	15	90	4.4	32	14.62	
5. B. H.	G	116	5.0	46.5	20.98	2	114	4.7	47	20.81	15	15	82	4.5	32	15.35	
6. S. S.	E	94	5.3	34	17.33	3	92	5.3	36	17.94	20	20	78	3.6	30	14.32	
7. J. T.*	G	92	4.2	34.5	17.45	2	98	4.4	35.5	18.09	20	20	92	4.2	33	15.52	
8. H. L.*	F	91	4.28	37	18.53	2	92	4.1	38	18.90	25	35	84	4.2	35	17.38	
9. C. P.*	F	100	4.95	40	18.01	2 1/4	102	4.9	40.5	17.98	13	13	94	4.5	38	14.48	
10. P. V.	P	98	4.4	38	16.78	2 1/2	91	4.5	37	17.04	42	48	78	4.0	34	14.44	
Ethylene + O <sub>2</sub> + Ether Anesthesia																	
11. D. G.	F	100	4.9	45	16.81	3 3/4	78	4.95	45	18.45	15	15	100	5.15	42	13.69	
12. P. A.	F	111	5.2	42	19.17	4 1/4	110	5.1	41	21.52	37	40	100	5.15	42	13.69	

\*Exploratory thoracotomy only.

See Table IV for explanation of abbreviations.

TABLE IV

STATE OF ARTERIAL BLOOD BEFORE, DURING, AND FOLLOWING TRANSPLURAL THORACIC SYMPLECTOMY IN 8 PATIENTS (14 OPERATIONS)

PATIENT	PREOPERATIVE					DURING OPERATION					POSTOPERATIVE						
	CONDI- TION	Hb. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	O.T. Hr.	Hb. (%)	R B.C.	HMCRT.	BLOOD O <sub>2</sub>	O <sub>2</sub> GIVEN			Hb. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>
											A	B					
<i>Ethylene + O<sub>2</sub> Anesthesia</i>																	
1. P. L.	P	92	4.46	38	16.44	2 1/4	90	4.4	36	13.95	14	15	4.6	30			12.52
2. P. L.	P	80	5.05	34	13.37	1 1/2	82	5.0	35	14.67	15	18	4.0	35			15.23
3. J. L.	G	100	5.1	35	18.82	1 3/4	96	4.9	34.5	18.96	20	20	5.0	35			17.79
4. D. M.	F	96	4.0	32	14.92	1 3/4	102	4.4	33	12.11	15	16	4.1	31			15.14
5. A. P.	P	70	4.2	27	10.91	2	74	4.3	30	11.26	15	15	3.8	28.5			10.65
6. A. P.	P	60	3.8	28.5	10.65	2	68	4.0	32	11.88	15	15	4.1	31			11.92
										During trans- fusion							
<i>Ethylene + O<sub>2</sub> + Ether Anesthesia</i>																	
7. V. M.	F	105	5.5	41	19.92	2 1/2	106	5.4	43	21.41	25	31	5.25	39			18.39
8. J. M.	F	92	4.8	36	16.90	2 1/4	90	4.7	36	17.00	28	25	4.4	33			13.10
9. C. C.	G	110	6.17	45	19.41	2 1/4	112	6.0	43	19.63	18	25	5.1	42			18.42
10. C. C.	G	90	5.1	42	18.42	2	90	5.0	40	17.33	18	24	4.8	40			16.91
<i>Ethylene + O<sub>2</sub> + Avertin Anesthesia</i>																	
11. H. M.	F	100	4.6	39	19.06	2 1/4	106	4.8	43	20.50	12	13	4.5	38			19.11
12. H. M.	F	92	4.5	38	19.11	2	102	4.7	30	16.04	25	27	4.9	39			17.04
13. V. M.	F	104	5.25	39	18.39	2	110	5.3	39	16.93	25	35	5.2	35.5			13.70
<i>Ethylene + O<sub>2</sub> + Vinethene Anesthesia</i>																	
14. D. M.	F	100	4.5	35.5	14.57	2 1/4	98	4.4	35	16.97	30	40	4.0	32			

During the operation, arterial blood was obtained just before closure of the pleural cavity. The condition of the patient is given as G—good, F—fair, or P—poor. Abbreviations: Hb., hemoglobin; R.B.C., red blood cells; Hmct., hematocrit; O<sub>2</sub>, oxygen; O.T., operating time in hours; oxygen given, A—average per cent during the entire operation, B—per cent of oxygen being given when arterial blood sample was obtained.

TABLE VII  
BRONCHIECTASIS; CONDITION OF THE ARTERIAL BLOOD BEFORE, DURING, AND FOLLOWING THE RESECTION OF LUNG TISSUE IN 10 PATIENTS

PATIENT	PREOPERATIVE					DURING OPERATION							POSTOPERATIVE					
	CONDIT- TION	HR. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	V.C.	O.T. (HR.)	HB. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	O <sub>2</sub> GIVEN		HR. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	
												A	B					
<i>Ethylene + O<sub>2</sub> Anesthesia</i>																		
1. M. G.	F	86	4.1	33	16.09	2100	2	82	4.0	30	10.92	10	14					
2. F. L.	P	98	4.38	37.5	18.16	3000	3 1/4	102	4.2	39	11.66	35	35					
3. F. M.	F	96	4.68	41	19.62	2900	2 1/4	104	4.7	42	12.44	20	25	86	4.5	30	14.17	
<i>Ethylene + O<sub>2</sub> + Ether Anesthesia</i>																		
4. D. G.	P	90	4.0	49	15.16	2100	2	94	4.5	50	13.31	37	38	90	3.9	44	14.00	
5. J. C.*	P	96	4.9	35	17.03	—	1 1/2	90	4.8	33	15.52	18	20	92	4.6	31	14.75	
6. M. S.	P	100	4.5	46	15.02	2600	2	105	4.8	47	14.77	20	25	95	4.2	42	15.97	
7. H. F.	G	85	4.3	46	15.51	2500	1 3/4	83	4.2	47	15.59	25	23	70	3.9	38	14.98	
8. D. H.	P	96	4.47	36	19.33	1900	2 3/4	94	4.4	35	12.88	40	32	80	4.0	30	12.88	
9. M. B.	P	90	4.9	37	16.07	1850	2	88	4.8	36	12.88	25	24	84	4.5	34	14.02	
10. G. N.†	P	94	4.75	35	14.79	1250	2	92	4.6	36	8.43	25	35	84	4.2	32	14.53	

\*Infected cystic disease of the lung.

†Bilateral chronic inflammation of the lung.

During the operation, arterial blood was obtained just before closure of the pleural cavity. The condition of the patient is given as G—good, F—fair, or P—poor. Abbreviations: HB., hemoglobin; R.B.C., red blood cells; Hmcrt., hematocrit; O<sub>2</sub>, oxygen; V.C., vital capacity; O.T., operating time in hours; Oxygen given, A—average per cent during the entire operation, B—per cent of oxygen being given when arterial blood sample was obtained.

TABLE VI  
CONDITION OF THE ARTERIAL BLOOD BEFORE, DURING, AND FOLLOWING A TRANSPLEURAL OPERATION FOR CARCINOMA OF THE LUNG

PATIENT	PREOPERATIVE					DURING OPERATION							POSTOPERATIVE				
	CONDI- TION	HB. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	O.T. (HR.)	HB. (%)	R B.C.	HMCRT.	BLOOD O <sub>2</sub>	O <sub>2</sub> GIVEN			HB. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>
											A	B					
<i>Ethylene + O<sub>2</sub> Anesthesia</i>																	
1. S.S.*	G	94	4.2	38.5	16.75	2	92	4.1	34	17.01	20	24		94	5.1	34	17.54
2. M.L.*	P	90	4.8	32	11.64	2 1/4	88	4.8	31	11.10	40	40					
3. W.E.	F	70	4.5	40	16.15	2 1/4	76	4.98	45	18.47	15	20					
4. F.F.	P	74	4.3	40	14.18	3	65	4.1	37	11.72	22	35					
<i>Ethylene + O<sub>2</sub> + Ether Anesthesia</i>																	
5. R.T.	G	100	4.8	32	15.83	2 3/4	105	4.8	38	12.83	41	45		110	5.2	42	14.35
6. E.B.*	F	105	5.1	56	16.85	1 1/2	108	5.3	58	18.18	25	28		100	4.4	52	17.56
7. J.K.	F	102	4.5	35	16.97	3	115	5.2	49	19.29	32	38					
8. R.T.	G	100	4.4	35	15.04	3	94	4.48	34.5	15.51	30	40		94	4.4	35	15.80
9. P.K.*	G	90	4.5	34	16.95	3	86	4.4	35	16.88	15	15		80	4.1	33	12.00

\*Exploratory thoracotomy only.  
See Table 13, p. 10.

\*Exploratory thoracotomy only.

See Table IV for explanation of abbreviations.



during the operation due to the marked anemia present. Patient No. 4 had considerable silicosis in both lungs and showed definite lowering in arterial blood oxygen during the operation despite the fact that the anesthetic mixture contained a high percentage of oxygen. No other patient in this group showed evidence of anoxia. The amount of oxygen in the anesthetic mixtures varied from 15 to 41 per cent. Except for patient No. 4 there was little difference between the preoperative and operative levels of oxygen in the arterial blood. The group was divided almost equally as to the anesthetic agents used, four receiving ethylene plus oxygen, and the remaining five, ethylene plus oxygen plus ether. With the exception of the influence of anemia and the poor general condition of the patients, there appeared to be little difference in arterial blood oxygenation between these two groups. The findings in the post-operative arterial blood samples will be discussed later.

*Bronchiectasis* (Table VII).—Although ten patients are included in this group, the diagnosis in patient No. 5 was infected congenital cystic disease of the lung and in patient No. 10 chronic inflammation of the lung (bilateral). Of all the groups of patients in this study the present group was by all odds the most difficult to manage from the standpoint of preventing anoxia. An analysis of Table VII revealed several factors contributing to this difficulty. The general condition of the patient was poor in most cases. Some of the patients had moderate to severe anemia. The vital capacity was definitely reduced in almost all, and extremely so in one (No. 10). In addition, most of these patients were more or less toxic due to the infection of the lungs. Patients Nos. 1, 2, 3, 4, and 10 had bilateral involvement of the lung. Only three of this group received ethylene plus oxygen as the anesthetic mixture, the remainder receiving ether in addition. Most of these patients were given a higher percentage of oxygen than those in the other groups in this study, the percentage of oxygen ranging from 15 to 40, the average being 27 per cent. In spite of this fact more patients of this group had a reduction in arterial blood oxygen during the operation (as compared to the pre-operative level) than those of any other group. In some cases this reduction was extreme, for example, patients Nos. 2, 3, 8, and 10. Cyanosis was observed in some of these patients

The duration of operation in this group averaged approximately two hours. Aspiration of secretions from the tracheobronchial tree, or waiting for improvement of the patient's condition before continuing with the operation, consumed a part of this time.

There was a noticeable difference in the behavior of the patients with unilateral infection as compared to those with involvement of both lungs. This is demonstrated by patients Nos. 5, 6, and 7 with unilateral involvement, who showed little or no reduction in arterial blood oxygen during the operation as compared to that of the preoperative levels. These patients were also less anemic and needed less oxygen during operation than the bilateral cases; thus indicating that the extent

TABLE VIII  
MISCELLANEOUS INTRATHORACIC OPERATIONS

PATIENT	PREOPERATIVE					DURING OPERATION					POSTOPERATIVE						
	CONDI- TION	HIB. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	O.T. (HR.)	HIB. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	O <sub>2</sub> GIVEN		HIB. (%)	R.B.C.	HMCRT.	BLOOD O <sub>2</sub>	
											A	B					
MEDIASITAL CYSTS OR TUMORS																	
<i>Ethylene + O<sub>2</sub> Anesthesia</i>																	
1. A. G.	G	92	4.1	38	16.85	2¼	90	4.3	37	15.36	23	29	78	4.0	34	14.48	
<i>Ethylene + O<sub>2</sub> + Ether Anesthesia</i>																	
2. E. S.	G	106	5.2	44	18.16	2	108	5.0	44	21.52	15	25	102	5.0	42	15.53	
3. L. C.	F	88	4.9	38	16.01	3¾	84	4.8	38	16.33	25	25	94	4.8	35	17.88	
OPERATIONS ON THE HEART OR GREAT VESSELS																	
<i>Ethylene + O<sub>2</sub> Anesthesia</i>																	
4. E. G.	F	98	5.2	38	19.30	3	100	5.0	37	17.34	18	19	80	4.0	30	12.41	
5. K. H.	F	90	5.0	37	18.12	2¾	90	4.9	36	14.85	13	13	70	4.0	26	11.58	
<i>Ethylene + O<sub>2</sub> + Ether Anesthesia</i>																	
6. S. C.	P	90	4.0	33	10.40*	2	90	4.0	33	14.60	34	36	100	3.8	32	15.91	
*Drawn during induction; patient was receiving 20 per cent oxygen. See Table IV for explanation of abbreviations.																	

\* Drawn during induction; patient was receiving 20 per cent oxygen.  
See Table IV for explanation of abbreviations.

anoxia or of reduction of arterial blood oxygen during the operation as compared to the preoperative level. On the other hand, the poor-risk patients (F. U. and M. L.) developed in one case marked reduction in blood oxygen during the operation as compared to the preoperative level and in the other a small reduction. The first of these patients was cyanotic; but the second, due to the anemia present, showed no evidence of cyanosis.

TABLE IX

INFLUENCE OF GENERAL CONDITION IN PRODUCTION OF ANOXIA

	GOOD				POOR			
	G. S. S. (V)		2. E. S. (VIII)		2. F. U. (VII)		2. M. L. (VI)	
	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.
Hb.	94	92	106	108	98	102	90	88
R.B.C.	4.2	4.1	5.2	5.0	4.4	4.2	4.8	4.8
Hemat.	38	34	44	44	37	39	32	31
Oxygen		24		28		35		40
Oxygen Av.		20		20		35		40
Blood O <sub>2</sub>	16.75	17.01	18.16	21.2	18.16	11.66	11.64	11.10

The patient's number, initials, and table from which taken are indicated. Note the lack of anoxia during operation in the good-risk patients as compared with the poor-risk cases.

Abbreviations: Hb., hemoglobin, R.B.C., red blood cells; Hemat., hematocrit; Oxygen, oxygen received by patient at the time the blood sample was drawn; Oxygen average, average percentage of oxygen received during the entire operation; Blood O<sub>2</sub>, arterial blood oxygen.

*Local Disease.*—As mentioned in the discussion of the results shown in Table VII patients with suppurative disease of the lung developed anoxia or at least a lowering of arterial blood oxygen during operation far more than patients with any other intrathoracic condition. These patients usually had some reduction in respiratory reserve. The disease condition had been present usually for a number of years, thus putting a strain on the heart. Most of these patients had a low-grade fever thus showing some degree of toxicity. All of these factors probably contributed in the reduction of tolerance to endure an intrathoracic operation. On the other hand, patients with mediastinal tumors or cysts, patients receiving operations for essential hypertension, and patients with carcinoma of the esophagus, cardia, or lung where no infection was present revealed little evidence of arterial blood oxygen reduction during an intrathoracic operation.

*Condition of the Blood.*—The results seen in Table X demonstrate the influence of anemia on arterial blood oxygen. The normal patient (C. P.) showed no change in the arterial blood oxygen taken during operation as compared to the preoperative reading, both being within the normal limits. This patient received an anesthetic mixture containing only 13 per cent of oxygen during the operation. Patients A. M. and A. P. showed a considerable anemia prior to operation, with marked reduction in arterial blood oxygen. Neither of these patients was cyanotic during the operation, although the arterial blood oxygen was under the cyanosis level, thus indicating that in anemic patients cyanosis is a poor sign to expect as an indication of anoxia. Unfortunately,

and distribution of the disease was the major factor in the marked lowering in blood arterial oxygen during operation in the bilateral cases.

The condition of the arterial blood following operation will be discussed later.

*Miscellaneous Intrathoracic Operations (Table VIII).—*

*Mediastinal Cysts or Tumors:* Only three patients were studied. The general condition was quite good in all three. The operation lasted an average of two and one-half hours. None of these patients were anemic and the preoperative arterial blood oxygen was fairly normal. There was little or no reduction in blood oxygen during the operation. The percentage of oxygen used in the anesthetic mixture averaged around 26. One of the three patients received ethylene plus oxygen, while in the other two ether was added. There was little difference noted between the two anesthetic mixtures with regard to the level of blood oxygen.

*Operations on the Heart and Great Vessels:* This group included two patients in whom partial pericardectomy was performed and in both cases the pleural cavity was opened. The third case was a transpleural ligation of a patent ductus arteriosus (and subacute bacterial endarteritis). Only the latter of these three revealed an anemia and this was quite marked. In the former two cases the blood oxygen was relatively normal prior to operation but in the latter (Case No. 6) the arterial blood oxygen was only 10.4 volumes per cent. In spite of this there was no cyanosis, due to the degree of anemia present. Following closure of the ductus, and before closing the pleural cavity, the arterial blood oxygen had become elevated about 45 per cent over the preoperative level.

One of the pericardectomies (patient No. 5) showed some lowering of blood oxygen during the operation. This patient had received ethylene plus 13 per cent oxygen as the anesthetic mixture.

The postoperative arterial blood values will be discussed later along with the other groups.

DISCUSSION OF RESULTS

It is obvious from the above presentation of the results obtained that several factors were contributory in the production of anoxia in these intrathoracic operations. Several of these factors were present in some of the groups of patients, whereas in others they appeared to be less prominent. In order to bring out the importance of various factors involved, a comparison of the results of blood studies in different patients was made.

*General Condition of the Patient.*—It is obvious from Table IX which presents the results in four patients, two designated as good risks and two as poor risks, that this factor alone plays a major role in the production of anoxia. With other factors being equalized as well as possible, the good-risk patients (S. S. and E. S.) revealed no evidence of

anoxia or of reduction of arterial blood oxygen during the operation as compared to the preoperative level. On the other hand, the poor-risk patients (F. U. and M. L.) developed in one case marked reduction in blood oxygen during the operation as compared to the preoperative level and in the other a small reduction. The first of these patients was cyanotic; but the second, due to the anemia present, showed no evidence of cyanosis.

TABLE IX  
INFLUENCE OF GENERAL CONDITION IN PRODUCTION OF ANOXIA

	GOOD				POOR			
	G. S. S. (V)		2. E. S. (VIII)		2. F. U. (VII)		2. M. L. (VI)	
	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.
Hb.	94	92	106	108	98	102	90	88
R.B.C.	4.2	4.1	5.2	5.0	4.4	4.2	4.8	4.8
Hemat.	38	34	44	44	37	39	32	31
Oxygen		24		28		35		40
Oxygen Av.		20		20		35		40
Blood O <sub>2</sub>	16.75	17.01	18.16	21.2	18.16	11.66	11.64	11.10

The patient's number, initials, and table from which taken are indicated. Note the lack of anoxia during operation in the good-risk patients as compared with the poor-risk cases.

Abbreviations: Hb, hemoglobin; R.B.C., red blood cells; Hemat., hematocrit; Oxygen, oxygen received by patient at the time the blood sample was drawn; Oxygen average, average percentage of oxygen received during the entire operation; Blood O<sub>2</sub>, arterial blood oxygen.

*Local Disease.*—As mentioned in the discussion of the results shown in Table VII patients with suppurative disease of the lung developed anoxia or at least a lowering of arterial blood oxygen during operation far more than patients with any other intrathoracic condition. These patients usually had some reduction in respiratory reserve. The disease condition had been present usually for a number of years, thus putting a strain on the heart. Most of these patients had a low-grade fever thus showing some degree of toxicity. All of these factors probably contributed in the reduction of tolerance to endure an intrathoracic operation. On the other hand, patients with mediastinal tumors or cysts, patients receiving operations for essential hypertension, and patients with carcinoma of the esophagus, cardia, or lung where no infection was present revealed little evidence of arterial blood oxygen reduction during an intrathoracic operation.

*Condition of the Blood.*—The results seen in Table X demonstrate the influence of anemia on arterial blood oxygen. The normal patient (C. P.) showed no change in the arterial blood oxygen taken during operation as compared to the preoperative reading, both being within the normal limits. This patient received an anesthetic mixture containing only 13 per cent of oxygen during the operation. Patients A. M. and A. P. showed a considerable anemia prior to operation, with marked reduction in arterial blood oxygen. Neither of these patients was cyanotic during the operation, although the arterial blood oxygen was under the cyanosis level, thus indicating that in anemic patients cyanosis is a poor sign to expect as an indication of anoxia. Unfortunately,

TABLE X

INFLUENCE OF DISEASE CONDITION ON THE PRODUCTION OF ANOXIA

	MEDIASTINAL TUMOR 1. A. G. (VIII)		HYPERTENSION 3. J. L. (IV)		CAR. OF THE LUNG 8. R. T. (VI)		BRONCHIEC- TASIS 3. F. M. (VII)	
	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.
Hb.	92	90	100	96	100	94	96	104
R.B.C.	4.1	4.3	5.1	4.9	4.4	4.4	4.7	4.7
Hemat.	38	37	35	34.5	35	34.5	41	42
Oxygen		29		20		40		25
Oxygen Av.		23		20		30		20
Blood O <sub>2</sub>	16.85	15.36	18.82	18.96	15.04	15.51	19.62	12.44

The patient's number, initials, and table from which taken are indicated. Anoxia was seldom observed during operation in the first three groups of patients but was often present in the bronchiectasis patients.

See Table IX for abbreviations.

it is in an anemic individual that early signs of anoxia must be recognized in order to prevent disastrous results. The blood oxygen during operation was actually slightly higher than the preoperative level, although the anesthetic mixture contained only 15 per cent oxygen.

*Anesthetic Agent.*—Most of the patients in this study received either ethylene plus oxygen or ethylene-oxygen plus ether. With the exception of the group in Table VII (bronchiectasis), little difference was noted between the two anesthetic mixtures in the maintenance of satisfactory blood oxygen during the operation. It was soon noticed that an increase in the percentage of oxygen given would not necessarily compensate for other factors which tended to produce anoxia. Ether added to ethylene-oxygen was of definite advantage in the production of deeper anesthesia without reduction of the percentage of oxygen below the desirable level. Taking the groups of patients as a whole, 17 to 20 per cent oxygen was found adequate for the prevention of anoxia.

*Influence of the Duration of the Operation on the Production of Anoxia.*—That long operations are much more poorly tolerated than short ones, an impression that has long been prevalent, was not substantiated by this study. When other factors which are influential in the production of anoxia were controlled, long operations were tolerated as well as the shorter ones. In this series of patients the operating time varied from approximately one and one-half to four hours. Examples of various durations of operation are as follows: (1) One and one-half hours, P. L. (No. 2), Table IV; (2) two hours, H. L. (No. 8), Table V; (3) three hours, P. K. (No. 9), Table VI, and (4) four hours, P. A. (No. 12), Table V. In each of the above four patients, oxygenation of the arterial blood near the end of the operation was as good or better than before the operation although the operation in patient No. 4 lasted almost three times as long as that of No. 1. In order to obtain these results, attention was given to the replacement of blood loss and to the maintenance of sufficient cardiorespiratory function.

It is fortunate that long operations may be well tolerated, for undue haste in some intrathoracic procedures would not be for the good of the patient.

TABLE XI

DECREASED O<sub>2</sub> TRANSPORTING MEDIA IN THE PRODUCTION OF ANOXIA

	NORMAL		ANEMIA			
	9. C. P. (V)		1. A. M. (V)		5. A. P. (IV)	
	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.
Hb.	100	102	76	80	70	74
R.B.C.	4.9	4.9	4.0	4.2	4.2	4.3
Hemat.	40	40	34	35	27	30
Oxygen		13		15		15
Oxygen Av.		13		15		15
Blood O <sub>2</sub>	18.01	17.98	12.57	13.81	10.91	11.26

Patient's number, initials, and table from which taken are indicated. A similar degree of anoxia before and during operation was observed in these patients.

See Table IX for abbreviations.

*Bronchial Obstruction and Decreased Vital Capacity.*—It has already been mentioned that intrathoracic operations for suppurative disease of the lung such as bronchiectasis and lung abscess were the least well tolerated in this series of patients. Three major factors play an important part in the production of anoxia in this group of patients, viz., (1) decreased vital capacity, (2) bronchial obstruction, and (3) some degree of toxicity. In addition, many of these patients have considerable anemia. In the group of ten patients studied the average preoperative arterial oxygen level was only 16.7 volumes per cent and in seven of these a fall of from 2 to 7 volumes per cent resulted during the operation in spite of the fact that a high per cent of oxygen was used in the anesthetic mixture, and that blood transfusions were being given during the operation. Several of these patients (five) had bilateral disease and in these the lowering of blood oxygen during operation was more severe. Some of these patients were not cyanotic and revealed no other obvious signs of anoxia until the blood was analyzed. When the preoperative blood oxygen is as low as 14 or 15 volumes per cent in the presence of an anemia an alarming degree of anoxia may result before obvious signs or symptoms are manifest.

Obstruction of the air passages during operation may be considerably obviated by postural drainage both before and during operation and by bronchoscopic aspiration at the conclusion of the operation. This routine has usually been used in our patients. In a few patients an endotracheal catheter was employed during the operation. In spite of the previously mentioned precautions, some obstruction of the air passages by secretions, blood, or pus is apt to occur and interfere with ventilation of the blood. Reduction in blood oxygenation by poor ventilation cannot be completely compensated for by increasing the percentage of oxygen in the anesthetic mixture used. Blades and Graham<sup>20</sup> have thought it advisable to elevate the head of the table during operation in patients with bilateral bronchiectasis. The secretions from the upper lobes then tend to drain into the lower lobe of the dependent side, thus keeping the trachea clear. At the conclusion of the operation, bronchoscopic aspiration of the accumulated secretions is carried out.

TABLE X

## INFLUENCE OF DISEASE CONDITION ON THE PRODUCTION OF ANOXIA

	MEDIASTINAL TUMOR 1. A. G. (VIII)		HYPERTENSION 3. J. L. (IV)		CAR. OF THE LUNG 8. R. T. (VI)		BRONCHIEC- TASIS 3. F. M. (VII)	
	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.
Hb.	92	90	100	96	100	94	96	104
R.B.C.	4.1	4.3	5.1	4.9	4.4	4.4	4.7	4.7
Hemat.	38	37	35	34.5	35	34.5	41	42
Oxygen		29		20		40		25
Oxygen Av.		23		20		30		20
Blood O <sub>2</sub>	16.85	15.36	18.82	18.96	15.04	15.51	19.62	12.44

The patient's number, initials, and table from which taken are indicated. Anoxia was seldom observed during operation in the first three groups of patients but was often present in the bronchiectasis patients.

See Table IX for abbreviations.

it is in an anemic individual that early signs of anoxia must be recognized in order to prevent disastrous results. The blood oxygen during operation was actually slightly higher than the preoperative level, although the anesthetic mixture contained only 15 per cent oxygen.

*Anesthetic Agent.*—Most of the patients in this study received either ethylene plus oxygen or ethylene-oxygen plus ether. With the exception of the group in Table VII (bronchiectasis), little difference was noted between the two anesthetic mixtures in the maintenance of satisfactory blood oxygen during the operation. It was soon noticed that an increase in the percentage of oxygen given would not necessarily compensate for other factors which tended to produce anoxia. Ether added to ethylene-oxygen was of definite advantage in the production of deeper anesthesia without reduction of the percentage of oxygen below the desirable level. Taking the groups of patients as a whole, 17 to 20 per cent oxygen was found adequate for the prevention of anoxia.

*Influence of the Duration of the Operation on the Production of Anoxia.*—That long operations are much more poorly tolerated than short ones, an impression that has long been prevalent, was not substantiated by this study. When other factors which are influential in the production of anoxia were controlled, long operations were tolerated as well as the shorter ones. In this series of patients the operating time varied from approximately one and one-half to four hours. Examples of various durations of operation are as follows: (1) One and one-half hours, P. L. (No. 2), Table IV; (2) two hours, H. L. (No. 8), Table V; (3) three hours, P. K. (No. 9), Table VI, and (4) four hours, P. A. (No. 12), Table V. In each of the above four patients, oxygenation of the arterial blood near the end of the operation was as good or better than before the operation although the operation in patient No. 4 lasted almost three times as long as that of No. 1. In order to obtain these results, attention was given to the replacement of blood loss and to the maintenance of sufficient cardiorespiratory function.

It is fortunate that long operations may be well tolerated, for undue haste in some intrathoracic procedures would not be for the good of the patient.



Thus, it is evident from the above studies that several factors may contribute to the production of anoxia both during and following intrathoracic operations. Also, that the ill effects of one or more factors might not be entirely compensated by improving the patient otherwise. Attention should be given to the various steps in the transportation of oxygen from the inhaled gas to the tissues and it should be ascertained that the organs are functioning properly before an operation is done. This will include transfusion of blood in patients with anemia, improvement of the nutritional state of patients with esophageal obstruction, and postural or bronchoscopic drainage for patients with pulmonary infection. During the operation, blood transfusion will maintain a more nearly normal oxygen transporting medium in the blood and postural drainage will help to maintain a patent airway.

The question of anesthesia mixtures continues to be a subject of considerable controversy. We are in agreement with Churchill and Beecher<sup>9</sup> that ether appears to have no more harmful effects than ethylene or cyclopropane in these patients. Since ethylene is rapid and pleasant for induction, is non-irritating, is administered in a physiologically normal amount of oxygen, and is undisturbing to the cardiac mechanism, we have considered it somewhat more advisable and have added ether vapor when indicated in sufficient amounts to obtain the desired depth of anesthesia. It has been well demonstrated by these recorded studies that a high percentage of oxygen in the anesthetic mixture does not necessarily mean that the blood oxygen levels will be correspondingly increased. From the studies made, it appeared that from 17 to 20 per cent oxygen in the anesthetic mixture was sufficient for satisfactory oxygenation of the blood in all except the patients with bronchiectasis or other suppurative processes of the lung. In these patients a higher percentage of oxygen is desirable, but it should not be the source of false security. To have administered 50 to 60 per cent of oxygen in the anesthetic mixture does not necessarily mean that the patient is able to make use of the oxygen received.

#### SUMMARY AND CONCLUSIONS

1. An investigation of the incidence of anoxia both during and following intrathoracic operations has been made in forty-five patients (fifty-one operations).
2. The operations were made for carcinoma of the lung (9); mediastinal tumors or cysts (3); malignant hypertension (8); constrictive pericarditis (2); bronchiectasis (10); carcinoma of esophagus or stomach (12), and patent ductus arteriosus (1).
3. Ethylene-oxygen or ethylene-oxygen plus ether anesthesia administered under mild positive pressure (4 to 8 mm. Hg) through a snug fitting face mask was employed in most cases.
4. Anoxia was seldom observed during the operation in patients who had no infection of the lung. Factors which played a major part in

TABLE XII

POSTOPERATIVE ANOXIA IN 4 PATIENTS WITH NORMAL BLOOD OXYGEN BEFORE AND DURING SURGERY

	12. P. A. (V)			4. S. C. (V)		
	PREOP.	OP.	P.O.	PREOP.	OP.	P.O.
Hb.	114	110	100	90	94	90
R.B.C.	5.2	5.1	5.2	4.3	4.7	4.4
Hemat.	42	41	32	40	40	32
Oxygen		40			15	
Oxygen Av.		37			15	
Blood O.	19.17	21.52	13.69	19.40	17.35	14.62
	1. A. G. (VIII)			5. B. H. (V)		
	PREOP.	OP.	P.O.	PREOP.	OP.	P.O.
Hb.	92	90	78	116	114	82
R.B.C.	4.1	4.3	4.0	5.0	4.7	4.5
Hemat.	38	37	34	46.5	47	32
Oxygen		29			15	
Oxygen Av.		23			15	
Blood O.	16.85	15.36	14.48	20.98	20.81	15.35

The patient's number, initials, and table from which taken are indicated. Twelve of forty-four patients studied, or 27.2+ per cent, showed similar results.

See Table IX for abbreviations.

*Postoperative Anoxia in Patients Having Normal Blood Oxygen Before and During Operation.*—In the above series of patients twelve of forty-four revealed a reduction in blood oxygen in the postoperative samples where the preoperative and operative blood oxygen was normal. Six of these were in the group of patients with carcinoma of the esophagus or stomach, three in the miscellaneous intrathoracic operations, two in the hypertension group, and one patient had bronchiectasis. The remaining seven of the fifty-one operations had no postoperative blood oxygen determinations. Except in the case of bronchiectasis most of the postoperative reduction in blood oxygen occurred in groups where little or no fall occurred during the operation. The significance of this is obvious in that a patient who appeared to have gone through an operation with little or no difficulty might be less observed during the postoperative period and the ill effects of the subsequent drop in blood oxygen be unobserved until serious consequences had occurred. In Table XII are presented data concerning four patients in whom reduction in blood oxygen occurred following operation although it had remained normal during the operation. It will be noted that this fall was extreme in three of the four cases, approximately 5 volumes per cent. Since the preoperative and operative levels were quite good in these cases, the postoperative fall led to no serious difficulties.

The explanation for this reaction was not entirely clear. It was accounted for in part by the oozing of blood within the pleural cavity following operation, but the amount of blood loss was insufficient to explain the degree of anoxia. Examination of the blood showed that it was due in part to the development of hypochromatic anemia. It was quite evident that the red cell count is least reliable for determining the state of the oxygen transportation media. The hemoglobin values were more reliable and the hematocrit most accurate in this regard.

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influencing the development of anoxia included: the general condition of the patient, the state of the blood, the local disease, bronchial obstruction, and decreased vital capacity.

5. The duration of the operation and the anesthesia appeared to have little influence on the production of anoxia when the above contributory factors were controlled. Ether when added to ethylene-oxygen produced deeper anesthesia with associated adequate oxygenation. The administration of a high percentage of oxygen in the anesthetic mixture may give a false sense of security if sufficient attention is not given to the other factors which play a part in the production of anoxia.

6. Of fifty-one operations, the blood oxygen level before, during, and following surgery remained normal in twenty-one, but was reduced during operation in fourteen. Postoperative reduction in blood oxygen with unchanged blood oxygenation during surgery was observed in twelve out of forty-four patients (27.2 per cent) in whom postoperative studies were made.

7. The hematocrit reading was a much better index than the red cell count or hemoglobin value for the determination of the true state of oxygen transporting medium.

8. There were six postoperative deaths, none apparently related to the anesthesia employed. Three deaths were on the basis of cardiac failure, a fourth was due to anuria following the use of sulfanilamide, a fifth was due to pneumonia following lobectomy on a very poor-risk child for bilateral bronchiectasis, and the sixth due to massive empyema with leak of the anastomosis following resection of the cardia.

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on dogs with suppuration in the left lung. This is introduced bronchoscopically by insufflating the foul sputum of bronchiectatic patients. It is hoped that this second group will allow a more critical evaluation of the effectiveness of this method, especially as to its clinical application.

Graham has stated that the virulent type of infection present is very instrumental in producing the high incidence of bronchopleural fistula postoperatively. He also emphasizes that if simultaneously total thoracoplasty could be done safely, in order to obliterate the potential empyema space, then he did not think that closure of the stump would continue to be anything of major importance. Rienhoff has reported the occurrence of bronchopleural fistula in sixteen of sixty-one total pneumonectomies or 26.2 per cent. Ochsner<sup>5</sup> has had a failure of closure of the stem bronchus in three of thirty-two total pneumonectomies for pneumoplastic diseases, with an incidence of approximately 9 per cent. Shenstone<sup>6</sup> has noted only one open fistula develop in twenty-three consecutive total pneumonectomies for a minimal  $\frac{1}{4}$  per cent. With the exception of the last two series cited, it is very obviously apparent that bronchopleural fistula in total pneumonectomy is still the important factor.

In this series of twenty-seven experimental pneumonectomies using a silver plug as a method of bronchial closure, there were five deaths. Only three were considered as resulting from the bronchus opening. In the other two the bronchus remained closed. The plug was removed bronchoscopically in the twenty-four animals surviving, at intervals varying from fourteen days to over twelve months. The three deaths due to the plug being coughed up by the animals happened within the first two weeks postoperatively. These fatalities occurred early in the series because silver plugs of correct size were not available and the plugs used were too small. In the last ten animals operated upon there have been no deaths.

#### EXPERIMENTAL TECHNIQUE

Normal dogs averaging approximately 8 kg. were operated upon under intraperitoneal nembutal and positive pressure anesthesia. Total left pneumonectomy was performed in twenty-seven animals using the following technique. The usual incision in the fourth left interspace was utilized, cutting across the fibers of the latissimus dorsi muscle; however, in the last five experiments the gridiron incision was used. The pulmonary vessels were individually and doubly ligated with a fine braided black silk. A purse string of silk was sutured around the left stem bronchus about 1 to 1½ cm. distal to the carina. A silver plug as described in Fig. 1 (A) was then inserted into the lumen of the stem bronchus through a 1 cm. transverse incision in the secondary bronchi. The purse string was then tied snugly around the groove in the middle third of the silver plug, before cutting away the entire left lung (Fig 1, B). The lung was removed 1 to 5 mm. distal to bifurcation of the stem bronchus. A flap of tissue 5 mm. in width by 4 mm. in length was

## SILVER PLUG AS A METHOD OF BRONCHIAL CLOSURE IN EXPERIMENTAL PNEUMONECTOMY

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THE lack of a method of permanently closing the stem bronchus was one of the most important factors in delaying the advent of the first successful total pneumonectomy for bronchiogenic carcinoma in 1933, which was performed by Graham.<sup>1</sup> In the past decade the operative mortality has steadily decreased from a relatively prohibitive 50 per cent to from 20 to 25 per cent in pneumonectomy, exclusively for bronchiogenic carcinoma. The latter mortality rate is for a series of cases of forty or more. Pneumonectomy for a smaller series of cases or one including other conditions carries an even lower operative mortality rate. Opening of the stem bronchus has been the major cause contributing to the excessively high mortality rate. A tremendous amount of experimental work has been done endeavoring to solve this problem. Rienhoff,<sup>2</sup> Adams,<sup>3</sup> and others have contributed to this problem both clinically and experimentally; the former has written a very comprehensive survey of the literature in his last publication.

Experimental methods to have even the slightest value must, if successful, be capable of metamorphosis into the realm of clinical usage and applicability. Following so closely upon Rienhoff's comprehensive monograph concerning closure of the bronchus in total pneumonectomy, it would seem very apparent that there is little to add. However, a review of the literature on bronchial closure and conclusions drawn from clinical and experimental work have pretty well settled two things. One, that most experimental work on this subject falls short because of not being clinically applicable; infection in the clinical cases and lack of the same in the dog's tracheobronchial tree is the essential difference. Two, healing of the bronchial stump occurs at a site of predilection which, in the great majority of instances, is the distal end of the bronchus, and this in spite of the type, number, or location of any or all varieties of occluding materials or tissues. The use of a silver plug as a method of bronchial closure after experimental lobectomy has been reported previously by Rosenthal and his associates.<sup>4</sup> In the present experimental work being reported it has been used as a method of bronchial closure after total left pneumonectomy in twenty-seven normal dogs. At the time of this presentation, similar experimental work is being carried out

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TABLE I

TOTAL LEFT PNEUMONECTOMY USING SILVER PLUG IN CLOSURE OF BRONCHUS

DOGS OPERATED	OPERATIVE DEATHS		MORTALITY (%)	
	BRONCHUS		BRONCHUS	
	OPENED	REMAINED CLOSED	OPENED	REMAINED CLOSED
27	3	2	11.1	7.4

2. The three deaths occurred six, twelve, and nineteen days post-operatively. The mechanism was apparently due to tension pneumothorax which occurred shortly after coughing up the plug at the times previously cited. These instances happened early in the series because silver plugs too small for the stem bronchus were used. Plugs of correct size were not available.

3. There have been no fatalities in the last ten animals operated upon.

4. The silver plug was removed bronchoscopically at intervals varying from fourteen days to more than twelve months.

5. Bronchoscopically there was rarely any sign of irritation or infection noted around the plug, either before or after removal.

6. The proximal end of the silver plug approximated the carina to within 2 or 3 mm. in all the animals surviving.

7. The plug was rotated with the extracting forceps before removal was attempted bronchoscopically. A small amount of traction was all that was necessary to loosen the plug and attached silk from its bed in the healed distal end of the bronchus. Both the silk purse string and the suture used to anchor the bronchial flap to the perforated distal end of the plug were found attached to the plug in the majority of cases. This agrees with other reports in the literature regarding the occluding sutures cutting through.

8. The areas where the sutures cut through were entirely healed grossly and microscopically.

9. The distal end of the bronchus after the plug was removed appeared clean and showed no evidence of infection. There was a small amount of oozing from the bronchial bed from which the plug was removed; however, this ceased spontaneously within a minute or two.

10. The dogs were sacrificed from three to twelve months postoperatively. In every case the bronchial stump was cone shaped and of homogeneous consistency throughout.

11. The heart and diaphragm in all animals had shifted into the pleural cavity of the operated side. The ribs on the left side were slightly compressed. (Fig. 3.)

12. Microscopically (Figs. 4, 5, and 6), the bronchial flap which was sutured to the perforation in the distal end of the plug protruded in to the lumen from the stump. The relationships of mucosa, cartilage, and muscle were the same in the wall of the bronchus as in the stump.

13. The wound in the chest wall was infected in six of the twenty-seven animals. In two of the animals that died, eight and five weeks

fashioned from the septum bifurcating cartilaginous portion of the stem bronchus and sutured to the distal end of the plug as in Fig. 2. The intrabronchial space distal to the silver plug was filled with sulfanilamide and closed with four mattress sutures of silk. About 3 Gm. of sulfanilamide were left in the pleural cavity before closing. No attempt was made to cover the end of the bronchus with mediastinal pleura. Two pericostal sutures of silk were tied and the wound closed in layers after overinflating the opposite lung. Two grams of sulfanila-



Fig. 1.—A, Lateral view of silver plug illustrating ridge on distal end with perforation for suturing membranous flap to (a); groove around distal third of plug (b); perforations in proximal third for drainage (c).

B, View of the proximal end as seen bronchoscopically, demonstrating crossbar necessary for removal (d).

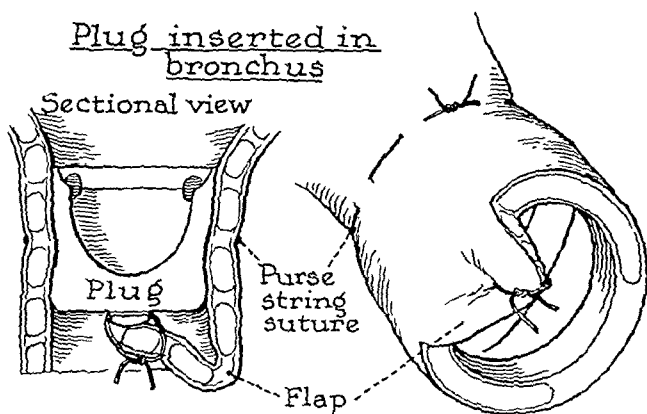


Fig. 2.—Sectional view of silver plug in stem bronchus; distal end of stem bronchus showing silver plug held in place by tied purse-string suture. Flap was fashioned from wall of bronchus as shown or septum bifurcating stem bronchus.

amide were spread throughout the wound proper. The cutaneous sutures were removed routinely on the eighth postoperative day. The silver plug was removed bronchoscopically at intervals post operatively, varying from fourteen days to more than twelve months.

#### RESULTS

1. Twenty-four of the twenty-seven normal dogs upon whom total left pneumonectomy was performed survived the operative procedure (Table I). Two additional deaths occurred secondarily to operation (see below).



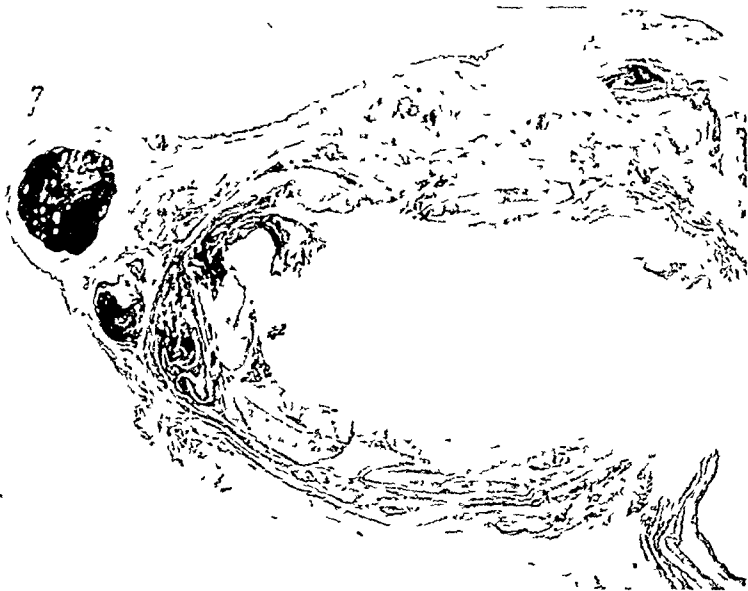


Fig 5—Low-power photomicrograph of left stem bronchus, showing narrowing of bronchial lumen proximal to site of silver plug. Retained black silk at distal end



Fig 6—High-power photomicrograph of left stem bronchus, as seen in Fig. 4, showing distal stump and bronchial flap with retained silk. Note definite layers of mucosa, muscle, and cartilage completely covering distal stump and united by a narrow zone of scar

postoperatively, the wound infection was interpreted as being responsible. These two deaths occurred five and three weeks, respectively, after removal of the plug. Autopsy revealed a healed and intact bronchial stump.

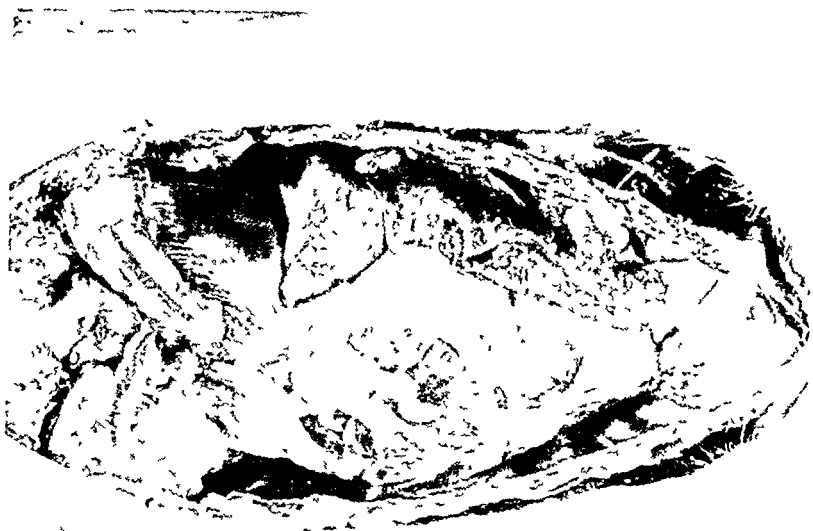


Fig. 3.—Post-mortem view with anterior chest wall removed in sacrificed animal, thirty days after plug removal, showing shift of heart and mediastinum to operated side.

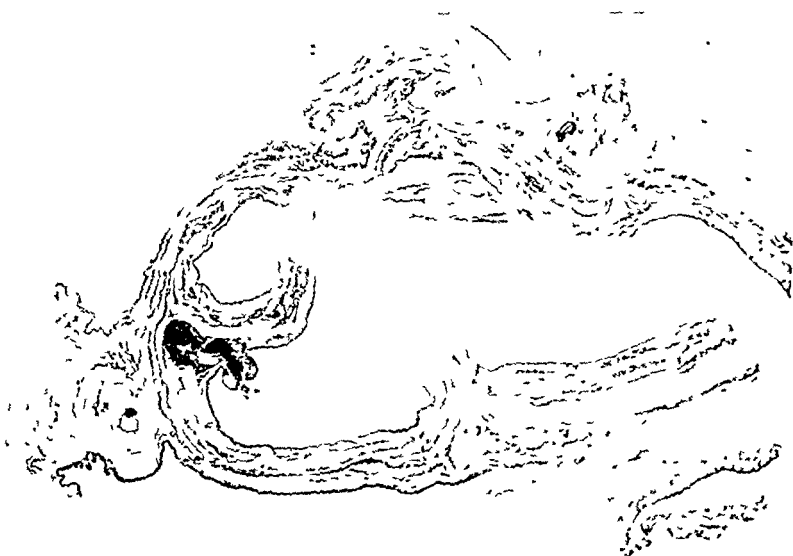


Fig. 4.—Low-power photomicrograph of left stem bronchus (30 days after pneumonectomy—plug removed on sixteenth day postoperatively) showing muscle, cartilage, and mucosa covering distal end and bronchial flap projecting into lumen.

need be to become solid, especially during the critical period after the occluding sutures cut through. The silver plugs have been left in many months without any apparent deleterious results.

The problem of the virulence of the infection clinically and whether or not the lowered plasma protein and ascorbic acid levels in patients with carcinoma of the lung will allow optimum healing conditions is another uncontrollable factor to be contended with, as emphasized by Graham. It is hoped that, by continuing these experiments in dogs with artificially produced purulent bronchitis, the value of the silver plug in an infected field will be proved or disproved.

Another method of support for the bronchial stump is the chest wall which will fall in after total or subtotal thoracoplasty as used by Graham on the first total pneumonectomy. However, he considers this unsafe as a simultaneous procedure. Whether a selective paravertebral thoracoplasty simultaneously over the stem bronchus will allow enough of the chest wall to fall in to act as a pedicle flap for adequate support is something for conjecture. Graham's original intention was to obliterate the pleural space entirely, in the absence of which an empyema could not form.

The deaths of the two animals which died as a result of wound infection, wound disruption, and open pneumothorax were attributed to the skin sutures being inadvertently left in the wound indefinitely. These deaths occurred three and five weeks after plug removal and were not considered operative deaths. The bronchial stumps in both were solidly healed.

It is our supposition, theoretically, that if occluding sutures and mediastinal pleura will allow a bronchopleural fistula incidence of 25 per cent or less after total pneumonectomy clinically, then the additional support offered by the silver plug plus a selective paravertebral thoracoplasty should decrease the incidence proportionately.

The blowing to-and-fro of air during respiration must be prevented to allow the all-important cut end time to heal. The marked accentuation of this unwanted mechanism by coughing during the critical period we consider might be better obviated by the addition of the silver plug and other supportive measures as mentioned.

In the twenty-four animals in which the plug remained intact postoperatively, no bronchopleural fistula occurred either before or after removal of the plug.

#### SUMMARY

1. Total left pneumonectomy was performed in twenty-seven normal dogs using a silver plug as a method of bronchial closure.

2. There were three postoperative deaths due to the plug being coughed up within two weeks postoperatively. These deaths occurred early and were due to the fact that the silver plug was too small and did not fit the bronchus snugly. Therefore, the plug must be of the correct size.

## COMMENT

Our experimental work agrees generally with that of others except for a few minor disagreements on the healing of the bronchus. It is offered as a constructive and supplemental addition to enhance the bronchial healing by allowing more time for the granulation tissue plug to become solid before being subjected to the stress of the intrabronchial pressure occasioned by coughing or sneezing. Based primarily on prophylaxis, the silver plug merely adds another bulwark or buttress to support the soft and easily disrupted plug of granulation tissue at the cut distal end. We believe that it might be used in addition to the occluding sutures and the mediastinal pleura in effecting a permanent closure of the stem bronchus in pneumonectomy clinically.

Rienhoff and his associates conclude that the main point of healing is at the cut end. They also state that every effort must be made to preserve the viability of this portion not only by gentle handling which avoids any sort of trauma, such as crushing, cauterization or suturing, but also by preserving the circulation of the bronchial artery. With reference to the latter our purse-string suture apparently does not jeopardize the circulation of the bronchial artery as the cut end of the stump still bleeds after it is tied, and the stump heals. All the bronchial stumps in our animals healed without the aid of mediastinal pleura, the cut end being left free in the pleural cavity. Obviously, in clinical cases the more items that can be used to act as a buffer or stopgap, as the occluding sutures are called, the better.

It is known both clinically and experimentally that the occluding sutures cut through the bronchial wall aided by infection and inflammatory edema after approximately ten days. This period corresponds to the time of occurrence of the opening of the bronchus and its subsequent bronchopleural fistula and empyema. It is during this critical period that we believe that the silver plug may serve as an additional so-called stopgap or buttress and protect the distal stump from "blowing out" after the occluding sutures cut through. Since the distal silk anchoring and purse-string sutures always cut through the bronchus, they are removed with the silver plug bronchoscopically and are still in its groove and perforation. The combination of these two factors plus inflammatory edema and granulations which have narrowed the bronchial lumen proximal to the silver plug have kept the plug in place in every animal except the three in which the plug was coughed up (Fig. 5). The silver plug used in the three dogs which died was much smaller than the stem bronchial lumen. It was thought that the increased intrabronchial pressure due to cough would be transmitted centrifugally through the silver plug to the lateral bronchial wall instead of being concentrated on the weakest part of the granulating stump distally, which like a chain is no stronger than its weakest link. If this is the mechanism and can be made to work clinically, then the distal stump should be protected as long as

## THE PROTEIN AND FLUID BALANCE IN EXPERIMENTAL SHOCK PRODUCED BY INTESTINAL TRAUMA

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A FUNDAMENTAL factor in the development of hematogenic shock is the decrease in the effective circulating blood volume. There is considerable discussion as to whether a local loss of fluid at the site of injury can account for the blood volume depletion. The experiments of Blalock<sup>1</sup> and Phemister and Parsons<sup>2</sup> support this hypothesis. The advocates of the "traumatic toxemia" theory<sup>3</sup> believe that there is a generalized as well as a local fluid loss, but definite evidence of a circulating toxin which initiates generalized capillary damage has not been demonstrated. Many investigators now believe that traumatic shock develops as a result of combined local and general fluid depletion, but have not found a specific cause.

In attempts to solve this problem, previous experiments have been concerned largely with fluid changes measured in terms of the increase in weight of the traumatized tissues. The nature and amount of the plasma protein lost from the circulation has received less attention. It is hence important that experiments be undertaken in which the plasma protein as well as the fluid loss be determined. The experiments which are described were performed in an effort to trace both the protein and fluid loss.

In experimental shock produced by standardized intestinal trauma it is possible to collect quantitatively the protein and fluid lost at the site of injury. In this type of shock most of the fluid and protein which are lost from the circulation can be recovered at the site of trauma. This loss occurs both from the serosal surface of the bowel and as extravasation into the bowel wall and its mesentery. The average protein concentration in the fluid lost from the bowel is 4.32 Gm. per cent. The fluid contains a proportionately greater amount of albumin than that found in the normal circulating plasma. The amount of plasma lost from the circulation increases proportionately with the survival time of the animal. The protein concentration of the plasma, and, hence, its specific gravity, decrease as shock develops.

In a previous publication a comparison was made of the relative efficacy of various concentrations of plasma in treating experimental shock due to intestinal trauma.<sup>4</sup> In these experiments, as in the current

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3. In the last ten animals there have been no fatalities.

4. The twenty-five dogs surviving total left pneumonectomy had the silver plug removed bronchoscopically at intervals postoperatively, varying from 14 to over 300 days.

5. After the silver plug had been removed bronchoscopically, the animals were sacrificed at different periods after removal to note the method and solidarity of the healed bronchial stump.

6. The distal end of the bronchus as seen through the bronchoscope after removal of the plug and as viewed through the pleural cavity post-mortem, appeared healed and revealed no sign of infection.

7. Bronchopleural fistula tested for in the usual manner was entirely negative. Microscopic sections verified the solidarity of the healing and the absence of infection.

8. Healing occurred at the line of suture in the distal end of the bronchus. The healed end of the bronchus was conical in shape in the majority of animals.

9. Two dogs died thirty-four and twenty-one days after removal of the plug from an infected wound. The bronchial stump was well healed and showed no sign of infection.

10. This experimental work is being continued with suppuration distal in the left lung.

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to a level of 60 to 70 mm. Hg several hours before death; in others, the pressure was maintained around 100 mm. Hg and fell precipitously immediately before death. As is shown in Table I, the dogs which survived the longest maintained the highest pressure. In spite of this tendency to maintain a more normal blood pressure the experiments with survival of more than eight hours showed the most marked increase in hematocrit and the greatest decrease in circulating plasma protein.

The concentration of circulating plasma protein and the specific gravity uniformly decrease in this type of shock. Table II tabulates the actual plasma protein concentration and plasma specific gravity in twenty-two typical experiments. The specific gravity decreases an average of .0015 from the control level to the last determination before the death of the animal. The plasma protein concentration falls an average of 13.77 per cent.

TABLE I  
SHOCK PRODUCED BY INTESTINAL TRAUMA

NUMBER OF EXPERIMENTS	SURVIVAL TIME (HR.)	RISE IN HEMATOCRIT (%)	DECREASE IN PLASMA VOLUME (%)	B.P. IN SHOCK (MM. HG)
5	2 to 7	19.6	35.8	45
9	7 to 8	19.4	42.2	85
6	8 to 10	23.3	51.9	98

TABLE II  
SHOCK PRODUCED BY INTESTINAL TRAUMA  
PLASMA-SPECIFIC GRAVITY AND PROTEIN CONCENTRATION; CONTROL AND SHOCK LEVELS

DOG NO.	INITIAL T.P. CONC.* (GM. %)	FINAL T.P. CONC. (GM. %)	PER- CENTAGE DECREASE	INITIAL SPECIFIC GRAVITY	FINAL SPECIFIC GRAVITY	DECREASE
41-285	5.87	5.58	4.9	1.0267	1.0267	0
41-369	5.57	4.98	10.6	1.0260	1.0250	0.0010
41-416	5.16	4.48	13.1	1.0245	1.0237	0.0008
41-446	5.56	4.82	13.3	1.0258	1.0242	0.0016
41-483	4.84	4.45	8.0	1.0247	1.0243	0.0004
41-511	5.96	5.21	12.5	1.0275	1.0257	0.0018
41-513	5.52	4.52	18.1	1.0263	1.0243	0.0020
41-499	6.79	5.39	20.6	1.0296	1.0258	0.0038
40-268	5.35	3.74	29.9	1.0250	1.0219	0.0031
41-455	5.79	3.39	3.5	1.0266	1.0256	0.0010
41-569	5.72	5.63	1.5	1.0262	1.0259	0.0003
41-551	5.09	4.44	12.8	1.0242	1.0228	0.0014
41-456	6.22	6.05	2.7	1.0271	1.0278	+0.0007
40-156	5.68	5.46	3.8	1.0256	1.0251	0.0005
41-527	5.38	4.30	20.0	1.0248	1.0212	0.0036
41-530	6.10	5.20	14.7	1.0271	1.0264	0.0007
41-556	5.31	4.71	10.7	1.0239	1.0226	0.0013
41-557	5.49	4.83	12.0	1.0240	1.0228	0.0012
41-478	5.93	4.49	22.0	1.0243	1.0233	0.0010
40-202	6.86	5.10	25.6			
10-388	6.56	5.16	21.3	1.0267	1.0227	0.0040
41-67	5.15	3.99	22.5	1.0230	1.0226	0.0004
Average			13.77			0.0015

\*Total protein concentration.

treatment of clinical shock, large amounts of plasma were used. An attempt has been made to determine the protein balance in treated dogs, but in the majority of experiments a large amount of the injected plasma cannot be accounted for at the site of trauma. Those animals treated with half-dilution plasma (plasma diluted with an equal quantity of saline solution) most closely approach a fluid and protein balance.

#### METHODS

All dogs were normal healthy animals obtained from stock. They were followed for a period of two weeks or more before the experiments in order to insure a normal food intake and fluid balance. The technique of the production of shock by intestinal trauma has been discussed at length in a previous publication.<sup>4</sup> Blood volumes were obtained using the blue dye, T-1824. All protein determinations were carried out in duplicate or triplicate by micro-Kjeldahl analysis. Specific gravity determinations were made by both gravimetric and falling-drop techniques, one method giving satisfactory check on the other. Bowel analysis was made in the following manner. After death of the animal, clamps were placed across the bowel and at the root of the mesentery in order to retain all blood and fluid in the traumatized area. The bowel was resected between clamps, transferred to a 3,000 c.c. beaker, and weighed. The bowel was then opened and all foreign material, including parasites, removed. About 2,000 c.c. of distilled water were then added followed by 75 c.c. of concentrated sulfuric acid. Digestion of this mixture was carried out overnight in a water bath followed by a 12-hour cooking over a low flame with constant mechanical stirring. At the end of this time a dark uniform mixture was obtained. This was analyzed for nitrogen by the macro-Kjeldahl procedure, the triplicate results agreeing within 0.5 per cent. Samples were then analyzed in triplicate for iron by a modification of the o-phenanthroline method of Schales using the photoelectric colorimeter. Close agreement was found between analysis of the crude digestion mixture and that found after digestion with nitric and perchloric acids. Using the results obtained in the iron determination the total amount of hemoglobin in the entire specimen could be determined. This was deducted from the total value of the bowel protein to allow for the red blood cells in the specimen. All balance studies included the total amount of protein and fluid lost from the serous surfaces, that lost into the bowel, and that removed in sampling.

#### EXPERIMENTAL OBSERVATIONS

The survival time of the average dog has varied considerably when shock is produced by intestinal trauma (Table I). Some animals have died two hours after trauma with the classical signs of shock, i.e., a rise in hematocrit, decrease in plasma volume, and a marked fall in arterial blood pressure. Others have survived ten hours or more. The arterial blood pressure always decreases as the shock state develops, but is subject to considerable variation. In some animals the pressure decreased



results with the albumin-globulin ratio of burn vesicle fluid (Table V) which also contains more albumin than the corresponding circulating plasma.

The protein content of the bowel and mesentery of ten normal dogs was determined as described under Methods. The results are shown in Table VI and, although there is considerable variation, only one dog (No. 41-451) showed an excessive discrepancy. The average bowel protein content was 4.15 Gm. per kilogram of body weight, or 0.188 Gm. per centimeter of bowel. The bowel protein calculated in terms of bowel length was most uniform and this figure has been used in determining protein balance tables.

TABLE V  
BLOOD PLASMA AND VESICLE FLUID IN BURNS

PLASMA				VESICLE FLUID			
T.P.	ALB.	GLOB.	A.-G.	T.P.	ALB.	GLOB.	A.-G.
5.99	3.92	2.07	1.4	3.46	2.78	0.68	4.1
5.62	3.42	2.20	1.5	2.94	2.69	0.25	10.7
5.94	3.19	2.75	1.16	4.64	3.34	1.30	2.6

TABLE VI  
PROTEIN CONTENT OF SMALL BOWEL AND MESENTERY IN NORMAL DOGS

DOG NO.	WEIGHT OF DOG (KG.)	T.P. BOWEL (GM.)	BOWEL PROTEIN (PER KG.)	LENGTH OF BOWEL (CM.)	BOWEL PROTEIN (PER CM.)
41-451	13.9	81.0	5.8	285	0.284
41-453	8.2	46.6	5.7	245	0.190
41-397	7.4	34.1	4.6	210	0.162
41-496	8.9	38.8	4.4	250	0.155
41-665	20.5	54.4	2.6	275	0.198
41-634	9.7	44.4	4.6	300	0.148
41-614	11.4	53.9	4.7	240	0.224
41-814	15.0	28.4	1.9	175	0.162
41-805	12.1	43.9	3.6	265	0.166
41-600	13.3	47.8	3.6	255	0.188
Average		49.0	4.15		0.188

The protein content of the traumatized bowel and mesentery at the time of death from shock is recorded in Table VII. There is a uniform increase over that of the normal bowel; the average total protein content was 62.9 Gm., compared with 49 Gm. in the normal. The traumatized bowel contained 4.76 Gm. of protein per kilogram of body weight and 0.216 Gm. per centimeter of bowel. The injured bowel contained less protein than the normal in only three instances.

Fluid and protein balances of the shock experiments are summarized in Tables VIII and IX. The decrease in plasma volume was calculated from the actual circulating plasma volume determined before and during the period of shock. The fluid recovered is the sum of that recovered from the bowel surface, the blood samples (plasma), and the increase

The relation of the albumin-globulin ratio of the circulating plasma protein to that of the protein present in the peritoneal fluid is tabulated in Table III. In all of the experiments the albumin-globulin ratio of the peritoneal fluid has been greater than that of the circulating plasma, indicating a preponderant loss of albumin. In twenty typical experiments recorded in Table III the albumin-globulin ratio of the peritoneal fluid is 1.69 times greater than the plasma. The total protein concentration of the fluid averages 4.32 mg. per 100 c.c. The very high protein concentration found in Dogs 41-483 and 41-551 has been, possibly, due to a technical error, but the Kjeldahl analyses were repeatedly checked and consistent results obtained. The albumin-globulin ratio of the peritoneal fluid formed during the first two hours of an experiment is greater than that formed between the third and seventh hour. An increasing amount of globulin is lost during the terminal phase of this type of shock (Table IV). It is of interest to compare the experimental

TABLE III

## SHOCK PRODUCED BY INTESTINAL TRAUMA

RELATION OF TOTAL PROTEIN, ALBUMIN, AND GLOBULIN IN PLASMA AND PERITONEAL FLUID

DOG NO.	PLASMA				PERITONEAL FLUID				PER CENT INCREASE
	T.P.	ALB.	GLOB.	A.-G.	T.P.	ALB.	GLOB.	A.-G.	
41-416	5.16	3.02	2.14	1.41	3.43	2.39	1.04	2.29	1.62
41-446	5.56	2.70	2.86	0.94	2.77	1.95	0.82	2.38	2.53
41-483	4.84	2.73	2.11	1.29	8.36	5.66	2.70	2.10	1.63
41-511	5.96	2.39	3.57	0.67	5.77	3.36	2.41	1.39	2.07
41-513	5.52	2.20	3.32	0.66	3.80	1.92	1.88	1.02	1.54
41-499	6.79	2.55	4.24	0.60	5.06	2.40	2.66	0.90	1.50
40-268	5.35	2.92	2.43	1.20	3.41	2.25	1.16	1.94	1.62
41-455	5.79	2.67	3.12	0.85	3.70	2.16	1.54	1.40	1.65
41-569	5.72	2.50	3.22	0.78	5.54	3.75	1.79	2.09	2.70
41-551	5.09	2.25	2.84	0.79	9.65	5.10	4.55	1.12	1.42
41-456	6.22	3.02	3.20	0.94	4.46	2.69	1.77	1.52	1.62
40-156	5.68	2.55	3.13	0.81	2.34	1.33	1.01	1.32	1.63
41-527	5.38	3.24	2.14	1.52	3.62	2.60	1.02	2.55	1.68
41-530	6.10	3.10	2.91	1.10	3.42	2.21	1.21	1.66	1.51
41-556	5.31	3.42	1.89	1.81	3.18	2.23	0.95	2.35	1.30
41-557	5.49	3.06	2.43	1.26	3.34	2.03	1.31	1.55	1.23
41-478	5.83	3.23	2.60	1.24	3.57	2.44	1.13	2.16	1.74
40-202	6.86	4.19	2.67	1.57	4.62	3.19	1.43	2.23	1.42
40-388	6.56	2.92	3.64	0.80	3.72	2.10	1.62	1.30	1.63
41-67	5.15	2.40	2.75	0.87	2.69	1.69	1.00	1.69	1.94
Average					4.32				1.69

TABLE IV

## SHOCK PRODUCED BY INTESTINAL TRAUMA

PERITONEAL FLUID	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	
2 Hr. post-trauma	4.62	3.19	1.43	Control shock
7 Hr. post-trauma	5.30	2.27	3.03	
2 Hr. post-trauma	5.10	3.68	1.42	Shock treated with plasma
7 Hr. post-trauma	5.34	4.11	1.23	

results with the albumin-globulin ratio of burn vesicle fluid (Table V) which also contains more albumin than the corresponding circulating plasma.

The protein content of the bowel and mesentery of ten normal dogs was determined as described under Methods. The results are shown in Table VI and, although there is considerable variation, only one dog (No. 41-451) showed an excessive discrepancy. The average bowel protein content was 4.15 Gm. per kilogram of body weight, or 0.188 Gm. per centimeter of bowel. The bowel protein calculated in terms of bowel length was most uniform and this figure has been used in determining protein balance tables.

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T.P.	ALB.	GLOB.	A.-G.	T.P.	ALB.	GLOB.	A.-G.
5.99	3.92	2.07	1.4	3.46	2.78	0.68	4.1
5.62	3.42	2.20	1.5	2.94	2.69	0.25	10.7
5.94	3.19	2.75	1.16	4.64	3.34	1.30	2.6

TABLE VI  
PROTEIN CONTENT OF SMALL BOWEL AND MESENTERY IN NORMAL DOGS

DOG NO.	WEIGHT OF DOG (KG.)	T.P. BOWEL (GM.)	BOWEL PROTEIN (PER KG.)	LENGTH OF BOWEL (CM.)	BOWEL PROTEIN (PER CM.)
41-451	13.9	81.0	5.8	285	0.284
41-453	8.2	46.6	5.7	245	0.190
41-397	7.4	34.1	4.6	210	0.162
41-496	8.9	38.8	4.4	250	0.155
41-665	20.5	54.4	2.6	275	0.108
41-634	9.7	44.4	4.6	300	0.148
41-614	11.4	53.9	4.7	240	0.224
41-814	15.0	28.4	1.9	175	0.162
41-805	12.1	43.9	3.6	265	0.166
41-600	13.3	47.8	3.6	255	0.188
Average		49.0	4.15		0.188

The protein content of the traumatized bowel and mesentery at the time of death from shock is recorded in Table VII. There is a uniform increase over that of the normal bowel; the average total protein content was 62.9 Gm., compared with 49 Gm. in the normal. The traumatized bowel contained 4.76 Gm. of protein per kilogram of body weight and 0.216 Gm. per centimeter of bowel. The injured bowel contained less protein than the normal in only three instances.

Fluid and protein balances of the shock experiments are summarized in Tables VIII and IX. The decrease in plasma volume was calculated from the actual circulating plasma volume determined before and during the period of shock. The fluid recovered is the sum of that recovered from the bowel surface, the blood samples (plasma), and the increase

The relation of the albumin-globulin ratio of the circulating plasma protein to that of the protein present in the peritoneal fluid is tabulated in Table III. In all of the experiments the albumin-globulin ratio of the peritoneal fluid has been greater than that of the circulating plasma, indicating a preponderant loss of albumin. In twenty typical experiments recorded in Table III the albumin-globulin ratio of the peritoneal fluid is 1.69 times greater than the plasma. The total protein concentration of the fluid averages 4.32 mg. per 100 c.c. The very high protein concentration found in Dogs 41-483 and 41-551 has been, possibly, due to a technical error, but the Kjeldahl analyses were repeatedly checked and consistent results obtained. The albumin-globulin ratio of the peritoneal fluid formed during the first two hours of an experiment is greater than that formed between the third and seventh hour. An increasing amount of globulin is lost during the terminal phase of this type of shock (Table IV). It is of interest to compare the experimental

TABLE III

## SHOCK PRODUCED BY INTESTINAL TRAUMA

RELATION OF TOTAL PROTEIN, ALBUMIN, AND GLOBULIN IN PLASMA AND PERITONEAL FLUID

DOG NO.	PLASMA				PERITONEAL FLUID				PER CENT INCREASE
	T.P.	ALB.	GLOB.	A.-G.	T.P.	ALB.	GLOB.	A.-G.	
41-416	5.16	3.02	2.14	1.41	3.43	2.39	1.04	2.29	1.62
41-446	5.56	2.70	2.86	0.94	2.77	1.95	0.82	2.38	2.53
41-483	4.84	2.73	2.11	1.29	8.36	5.66	2.70	2.10	1.63
41-511	5.96	2.39	3.57	0.67	5.77	3.36	2.41	1.39	2.07
41-513	5.52	2.20	3.32	0.66	3.80	1.92	1.88	1.02	1.54
41-499	6.79	2.55	4.24	0.60	5.06	2.40	2.66	0.90	1.50
40-268	5.35	2.92	2.43	1.20	3.41	2.25	1.16	1.94	1.62
41-455	5.79	2.67	3.12	0.85	3.70	2.16	1.54	1.40	1.65
41-569	5.72	2.50	3.22	0.78	5.54	3.75	1.79	2.09	2.70
41-551	5.09	2.25	2.84	0.79	9.65	5.10	4.55	1.12	1.42
41-456	6.22	3.02	3.20	0.94	4.46	2.69	1.77	1.52	1.62
40-156	5.68	2.55	3.13	0.81	2.34	1.33	1.01	1.32	1.63
41-527	5.38	3.24	2.14	1.52	3.62	2.60	1.02	2.55	1.68
41-530	6.10	3.19	2.91	1.10	3.42	2.21	1.21	1.66	1.51
41-556	5.31	3.42	1.89	1.81	3.18	2.23	0.95	2.35	1.30
41-557	5.49	3.06	2.43	1.26	3.34	2.03	1.31	1.55	1.23
41-478	5.83	3.23	2.60	1.24	3.57	2.44	1.13	2.16	1.74
40-202	6.86	4.19	2.67	1.57	4.62	3.19	1.43	2.23	1.42
40-388	6.56	2.92	3.64	0.80	3.72	2.10	1.62	1.30	1.63
41-67	5.15	2.40	2.75	0.87	2.69	1.69	1.00	1.69	1.94
Average					4.32				1.69

TABLE IV

## SHOCK PRODUCED BY INTESTINAL TRAUMA

PERITONEAL FLUID	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	
2 Hr. post-trauma	4.62	3.19	1.43	Control shock
7 Hr. post-trauma	5.30	2.27	3.03	
2 Hr. post-trauma	5.10	3.68	1.42	Shock treated with plasma
7 Hr. post-trauma	5.34	4.11	1.23	

TABLE IX

SHOCK PRODUCED BY INTESTINAL TRAUMA; PROTEIN BALANCE IN UNTREATED ANIMALS

DOG NO.	DECREASE IN CIRCULATING TOTAL PROTEIN (GM.)	PROTEIN RECOVERED FROM			PROTEIN BALANCE	
		PERITONEAL FLUID (GM.)	BOWEL (GM.)	BLOOD SAMPLE (GM.)	NEGATIVE	POSITIVE
41-369	26.4	8.80	8.4	1.65		7.55
41-423	15.4	10.16	12.85	1.26	8.87	
41-416	29.1	11.43	42.2	1.65	26.18	
41-446	13.7	13.65	5.7	1.48	7.13	
41-483	8.0	8.62	4.3	2.12	7.04	
41-513	18.2	5.7	6.7	2.06		3.74
41-499	8.5	6.01	0	2.31		0.18
40-268	12.6	9.58	12.1	2.06	11.14	
41-455	25.2	17.0	9.2	1.65	2.65	
41-551	13.7	22.2	17.62	1.5	27.62	
41-456	17.9	2.23	0	1.5		14.17
40-156	33.4	6.68	11.0	2.2		13.52
41-527	23.8	7.24	32.74	2.2	18.38	
41-530	26.1	6.70	4.24	1.81		13.35
41-556	13.7	4.6	0	1.76		7.31
41-455	16.4	5.3	1.6	1.54		7.96
41-478	14.7	10.7	29.58	0.79	26.37	
41-796	25.4	11.4	6.1	2.42		5.43
41-864	11.4	9.13	27.0	2.42	27.15	
Total					162.53	73.24

in the bowel weight. The normal bowel weighed an average of 25.6 Gm. per kilogram of body weight, and the traumatized bowel 36.1 Gm. per kilogram. Thirteen of the twenty dogs showed a negative fluid balance, i.e., more fluid was collected in the bowel than was lost in the circulating plasma. Seven dogs had a positive fluid balance. The average loss of fluid in the former group was greater than the retention in those having a positive balance. The possibility of error in these calculations is very great, but they indicate that in general the fluid lost from the circulation can be recovered at the site of trauma.

The protein balance (Table IX) is recorded in the same manner as the fluid balance. Ten dogs had a negative, and nine a positive, balance. The animals that lost more protein at the site of trauma than from the circulating plasma showed a greater protein imbalance than the others. The largest amount of protein lost in excess of the calculated decrease in plasma protein was 27.62 Gm. The largest amount of protein retained was 14.17 Gm.

Tables X and XI are summaries of fluid and protein balances in typical shock experiments when the animals were treated by intravenous injection of plasma in varying dilutions.\* In the fluid balance the total plasma available is the sum of the initial plasma volume and the volume of plasma injected. The fluid collected is determined in the same manner as previously described. The protein balance was obtained in the same manner. The animals treated with one-half dilution plasma (equal parts plasma and saline solution) had a very small retention of fluid and

TABLE VII

SHOCK PRODUCED BY INTESTINAL TRAUMA; PROTEIN CONTENT OF TRAUMATIZED BOWEL

DOG NO.	WEIGHT OF DOG (KG.)	TOTAL PROTEIN BOWEL	BOWEL PROTEIN (KG.)	LENGTH OF BOWEL (CM.)	BOWEL PROTEIN (PER CM.)
41-285	12.5			330	
41-383	14.9	62.7	4.2	330	0.190
41-369	12.0	87.7	7.3	300	0.292
41-423	15.7	64.4	4.1	293	0.219
41-416	13.9	109.9	7.9	360	0.305
41-446	14.8	53.5	3.6	315	0.170
41-483	9.5	49.3	5.2	285	0.191
41-511	12.6	64.6	5.1	300	0.215
41-513	8.8	60.3	6.8	285	0.211
41-499	9.3	43.6	4.7	270	0.162
40-268	10.0	55.9	5.6	233	0.240
41-455	17.7	76.9	4.3	360	0.213
41-569	12.6	66.3	5.3	300	0.221
41-551	11.8	61.8	5.2	235	0.252
41-456	18.5	57.9	3.5	308	0.188
40-156	11.9	36.0	3.0	250	0.144
41-527	14.6	83.5	5.7	270	0.309
41-530	14.8	55.0	3.7	270	0.204
41-556	10.0	27.3	2.7	210	0.124
41-557	11.2	46.0	4.1	264	0.174
41-455	12.1	51.3	4.2	265	0.194
41-478	19.3	88.6	4.6	315	0.282
41-796	17.4	59.7	3.4	285	0.209
41-864	16.0	85.5	5.3	310	0.276
Average		62.9	4.76		0.216

TABLE VIII

SHOCK PRODUCED BY INTESTINAL TRAUMA; FLUID BALANCE IN UNTREATED ANIMALS

CIRCULATING PLASMA VOLUME					FLUID RECOVERED			POSITIVE BALANCE	NEGA- TIVE BALANCE
DOG NO.	CON- TROL	SHOCK	DE- CLASE	FLUID RECOV- ERED	PERITO- NEAL FLUID	BLOOD SAMPLES	BOWEL WALL		
41-285	748	335	413	466	300	40	126		53
41-369	868	442	426	294	150	30	114	132	
41-423	710	315	395	515	380	23	112		120
41-416	856	337	519	479	310	32	137	40	
41-446	699	522	177	542	402	25	115		365
41-483	490	352	138	268	125	35	108		130
41-513	560	280	280	293	150	35	108		13
41-499	385	318	67	253	110	40	103		186
40-268	401	238	163	404	280	35	89		241
41-455	868	449	419	612	445	30	137		193
41-551	457	217	240	324	210	25	89		84
41-456	666	389	277	192	50	25	117	85	
40-156	894	319	575	420	285	40	95	155	
41-527	714	339	375	343	200	40	103	32	
41-530	643	252	391	332	196	33	103	59	
41-556	483	254	229	257	145	32	80		28
41-455	642	371	271	243	115	28	100	28	
41-478	773	677	96	430	300	15	115		334
41-796	880	483	397	478	325	45	108		81
41-864	802	557	245	422	260	44	118		177

vasomotor center fails and the circulation collapses. This same reaction may be repeatedly observed when dealing with patients, and the fallibility of the blood pressure as a sign of shock has been emphasized.

The changes in the circulating protein during the development of shock are very definite. The concentration of circulating total protein, and thus the plasma specific gravity, decrease. This can be due to one of two factors, either dilution of the plasma with interstitial fluid or a loss of plasma from the circulation. The actual mechanism is probably very complex and involves both factors. It is evident that a large amount of fluid and protein are lost at the site of trauma, but since this fluid contains less protein than plasma there must be some dilution of remaining plasma by reserve body water.

The albumin-globulin ratio of the peritoneal fluid is always greater than the circulating plasma. This indicates a greater proportional loss of albumin than globulin, and corresponds to the loss of protein in the vesicle fluid of burns and in shock produced by peritoneal cooling.<sup>5</sup> Also in these experiments an increasing amount of globulin is present in the peritoneal fluid when the animal is approaching death. A plausible explanation is that with some increased capillary permeability early in shock the smaller albumin molecule is able to escape. As shock progresses the permeability increases and the larger globulin molecule can also pass through the capillary wall. In these experiments the increased capillary permeability occurs at the site of trauma, but a general change in the capillaries can in no way be excluded.

The amount of fluid and protein which is lost from these animals is the sum of that fluid which oozes from the serous surface of the bowel and that amount which is present in the bowel wall and adjacent mesentery. The fluid which escapes can be measured accurately as to volume and protein content. That portion in the bowel and mesentery is determined by relative comparison of normal and traumatized bowel weight and protein, deducting a correction for hemoglobin. There may well be a considerable possibility of error in using an average figure for normal bowel protein, but the value used does approximate the mean of that found in all control animals. The bowel protein content of the animals in shock was consistently greater than that of the controls. In ten animals more protein was recovered at the site of trauma than could be calculated as lost from the circulating plasma. Less protein was recovered at the site of trauma in nine dogs. If all the protein is lost at the site of trauma one would expect to recover the total which disappears from the circulation. In many experiments considerably more protein is recovered. The possible origin of this is from a mobilization of reserve protein stores. This does not agree with Ebert and his co-workers<sup>3</sup> who feel that protein stores cannot be mobilized following shock from hemorrhage.

In the nine dogs in which all the protein could not be recovered only three showed a significant retention. The results in these nineteen dogs

TABLE X

SHOCK PRODUCED BY INTESTINAL TRAUMA; FLUID BALANCE IN TREATED ANIMALS

DOG NO.	INITIAL PLASMA VOL. (C.C.)	PLASMA INJECTED I.V. (C.C.)	TOTAL PLASMA AVAILABLE (C.C.)	FINAL PLASMA VOLUME (C.C.)	VOLUME PERITONEAL FLUID (C.C.)	BOWEL FLUID AND BLOOD SAMPLES	TOTAL FLUID ACCOUNTED FOR	BALANCE	REMARKS
40-324	650	600	1250	555	410	150	1115	135	Dilute plasma
40-202	805	600	1405	950	400	150	1500	95	Dilute plasma
40-180	1128	350	1478	592	300	140	942	536	Whole Plasma
40-294	908	1060	1968	618	370	150	1138	830	Whole plasma
40-447	738	65	803	455	470	165	1070	267	4x Conc. plasma

TABLE XI

SHOCK PRODUCED BY INTESTINAL TRAUMA; PROTEIN BALANCE IN TREATED ANIMALS

DOG NO.	INITIAL TOTAL CIR- CULATING PROTEIN (GM.)	PROTEIN INJECTED (GM.)	TOTAL PROTEIN (GM.)	FINAL TOTAL CIR- CULATING PROTEIN (GM.)	PERITONEAL FLUID PROTEIN (GM.)	BOWEL AND BLOOD SAMPLES	TOTAL	BALANCE
40-324	36.2	16.5	52.7	24.4	9.3	12.75	46.45	6.25
40-202	55.2	16.5	71.7	48.2	18.4	12.75	79.35	7.65
40-180	77.2	12.25	89.45	26.0	14.37	12.0	52.37	37.08
40-271	62.7	55.0	117.7	35.4	20.8	12.75	68.95	48.75
40-447	40.0	25.0	65.0	21.0	24.0	12.47	57.47	17.53

protein. These animals also showed the best response to treatment. The dogs treated with large amounts of whole plasma and four times concentrated plasma retained large amounts of fluid and protein. These dogs did not respond as well to treatment. A large amount of the plasma which disappeared from the circulation could not be accounted for at the site of trauma.

## DISCUSSION

The arterial blood pressure is not always a satisfactory criterion by which the severity of the shock state may be evaluated in the experimental animals. The arterial tension may be maintained at a near normal level for many hours during which the animal has a marked increase in the hematocrit and a reduced circulating plasma volume. In such an animal the pressure is often maintained until immediately before death and then may fall precipitously. Experience gained from these experiments again accentuates the impression that the development of shock requires a period of time, and that regardless of the blood pressure a progressive chain of events is instigated by the trauma. The maintenance of the pressure in some animals is probably due to narrowing of the circulatory bed by peripheral vasoconstriction until the



vasomotor center fails and the circulation collapses. This same reaction may be repeatedly observed when dealing with patients, and the fallibility of the blood pressure as a sign of shock has been emphasized.

The changes in the circulating protein during the development of shock are very definite. The concentration of circulating total protein, and thus the plasma specific gravity, decrease. This can be due to one of two factors, either dilution of the plasma with interstitial fluid or a loss of plasma from the circulation. The actual mechanism is probably very complex and involves both factors. It is evident that a large amount of fluid and protein are lost at the site of trauma, but since this fluid contains less protein than plasma there must be some dilution of remaining plasma by reserve body water.

The albumin-globulin ratio of the peritoneal fluid is always greater than the circulating plasma. This indicates a greater proportional loss of albumin than globulin, and corresponds to the loss of protein in the vesicle fluid of burns and in shock produced by peritoneal cooling.<sup>2</sup> Also in these experiments an increasing amount of globulin is present in the peritoneal fluid when the animal is approaching death. A plausible explanation is that with some increased capillary permeability early in shock the smaller albumin molecule is able to escape. As shock progresses the permeability increases and the larger globulin molecule can also pass through the capillary wall. In these experiments the increased capillary permeability occurs at the site of trauma, but a general change in the capillaries can in no way be excluded.

The amount of fluid and protein which is lost from these animals is the sum of that fluid which oozes from the serous surface of the bowel and that amount which is present in the bowel wall and adjacent mesentery. The fluid which escapes can be measured accurately as to volume and protein content. That portion in the bowel and mesentery is determined by relative comparison of normal and traumatized bowel weight and protein, deducting a correction for hemoglobin. There may well be a considerable possibility of error in using an average figure for normal bowel protein, but the value used does approximate the mean of that found in all control animals. The bowel protein content of the animals in shock was consistently greater than that of the controls. In ten animals more protein was recovered at the site of trauma than could be calculated as lost from the circulating plasma. Less protein was recovered at the site of trauma in nine dogs. If all the protein is lost at the site of trauma one would expect to recover the total which disappears from the circulation. In many experiments considerably more protein is recovered. The possible origin of this is from a mobilization of reserve protein stores. This does not agree with Ebert and his co-workers<sup>3</sup> who feel that protein stores cannot be mobilized following shock from hemorrhage.

In the nine dogs in which all the protein could not be recovered only three showed a significant retention. The results in these nineteen dogs

tend to indicate that in most of the animals the protein lost from the circulation can be accounted for at the site of trauma. There is a similar tendency for all of the fluid lost to be found in the same area (Table VII). It must be emphasized that this occurs in a specific type of shock (intestinal trauma) and these results do not necessarily apply to shock from other causes.

It is very difficult to interpret the significance of the fluid and protein balance records in this type of shock when treated with varying dilutions of plasma. The total amount of plasma injected could not be accounted for in any of the experiments. The most satisfactory therapeutic results were obtained in the animals treated with dilute plasma (equal parts plasma and saline solution). In these experiments the fluid and protein balance was most nearly equal. In other experiments, using large amounts of whole and four times concentrated plasma, a large amount of fluid and protein did not appear at the site of trauma. Less satisfactory therapeutic results were obtained in these animals. The loss of fluid and protein could be explained by a trapping in the circulatory bed or extravasation from the circulation because of a generalized increase in capillary permeability. It is of interest that the liver, spleen, kidneys, and lungs of these animals showed the minimum congestion previously described in control animals.\*

There has been no opportunity as yet to attempt to determine the fate of the lost plasma. A comparison of the wet and dry weights of organs of normal and shocked animals has not been helpful. At most, a very small amount of this protein appears in the urine. A very small amount of urine is excreted during the experiments and this rarely contains albumin.

#### SUMMARY

The results of these experiments indicate that progressive capillary damage results from the trauma to the bowel wall and this allows fluid containing protein to pass through the wall. In the first stages the smaller albumin molecule readily passes through the capillary wall, but as shock progresses the permeability increases. During the later and terminal stages the globulin passes out of the capillaries in increasing amounts. In these experiments this change in capillary permeability probably occurs primarily at the site of trauma. In balance studies on untreated shock of this type it is not necessary to postulate fluid and protein losses other than at the focus of injury. That a generalized capillary permeability can develop is indicated by the large amount of unrecovered fluid in the animals treated with plasma.

#### CONCLUSIONS

1. Fluid and protein shifts have been studied in experimental shock produced by intestinal trauma.
2. The plasma specific gravity and protein concentration decrease as the shock progresses.

3. The albumin-globulin ratio of the fluid recovered at the site of trauma is greater than that of the circulating plasma.

4. More albumin is lost in the early phase of shock; more globulin in the terminal phase.

5. The major proportion of fluid and protein lost from the circulation can be recovered at the site of trauma when the shock is not treated. This is not true when the shock is treated with plasma.

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#### CONCLUSIONS

1. Fluid and protein shifts have been studied in experimental shock produced by intestinal trauma.
2. The plasma specific gravity and protein concentration decrease as the shock progresses.

It was decided to test the tolerance of tissues to various substances which might be used as drains. Pieces of tubular and sponge rubber were implanted into the thigh muscles of three dogs. Uniformly, supuration occurred and one of the animals died of this cause. Glass was not tried because of fear of breakage if used in clinical cases. In a search for some unbreakable glass, a composition, "lucite"\* was found. After remaining for four weeks in apposition to an implanted piece of this material, the muscle of a dog's thigh showed no gross or microscopic evidence of inflammatory reaction. A narrow border of fibrosis (1.5 mm.) surrounded the foreign body, and a layer of flattened cells suggesting endothelium lay on the surface of the tissue (Fig. 2). From ten days after implantation of this material the dog showed no evidence of local tenderness or heat. It was therefore decided to use lucite in a few clinical cases.



Fig. 1.—Roentgenogram of a humerus in the quiescent stage of chronic osteomyelitis. There is no drainage, but the patient has pain at times. Note the areas of rarefaction and the areas of increased density.

This material proved particularly useful for the purpose in mind, for it can be molded and bent at will when immersed in boiling water, and it is difficult, though not impossible, to break.

Vitallium was considered as a nonirritating material, and has been reconsidered since Pearse has used it successfully in other locations than bone and has shown that there is very little tissue reaction to it in the common bile duct. It was not used in the present instance for the reason that it cannot be worked at the operating table to suit the individual case.

*The Configuration of the Drains.*—In order to provide an adequate drainage tract, one that should prevent the accumulation of pus and

\*Manufactured by E I du Pont de Nemours Co., Arlington, N. Y.

# PROLONGED DEPENDENT DRAINAGE WITH "LUCITE" DRAINS IN THE TREATMENT OF CHRONIC OSTEOMYELITIS\*

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(From the Department of Surgery, University of Minnesota)

ONE hundred thirty-three cases of hematogenous osteomyelitis have been seen at the University of Minnesota Hospitals in the past five years.<sup>2</sup> Forty-four of these were seen and treated at this clinic in the acute stage, and the only therapy which thus far has resulted in healing directly from the acute stage is oral sulfathiazole administration, with or without local implantation as well.<sup>4</sup> The great majority of the cases became chronic, and therapy in this stage of the disease has been widely varied. The use of maggots, as introduced by Baer, and of the Carrel-Dakin technique have not been tried in recent years here. On the orthopedic and general surgical services, between which these cases are divided, the Orr treatment has been used in a small number of cases, with successful wound healing in more than half. The policy for several years was expectant in character, without intervention unless abscess formation, pain, or sequestrum formation appeared.<sup>10</sup> Healing with cessation of drainage under this regimen occurred in only one-quarter of the cases.

Despite the moderate number of lesions which have ceased to drain or cause pain or fever, the impression remains that no standard method of treatment of chronic osteomyelitis has been demonstrated to lead to healing of a permanent nature. The patient in case after case has returned with an exacerbation months or even years after apparently complete healing had occurred.

Examination of the roentgenograms of bones of patients treated in the manners described reveals, even in the period of quiescence, areas of rarefaction highly suggestive of bone abscesses, areas of gross irregularity, and areas of markedly increased radiopacity (Fig. 1). Such pictures imply quiescence rather than a true return to normal function and architecture.

*The Choice of Drainage Material.*—Because of this failure in the handling of the chronic disease, Wangenstein suggested three and one-half years ago that a trial be given to prolonged dependent drainage and also that a tubular drain of some such nature as the glass abdominal drains formerly used in some European clinics be given a trial.

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debris, tubular drains were fashioned. Rather small ones were used early, but they tended to become plugged, and the standard size now is 1 cm. in external diameter, 7 mm. in internal diameter, and of a variety of lengths, with a flange 18 mm. in diameter and 3 mm. thick at one end. Holes were drilled in the flange for fixation (Fig. 3).

Sterilization caused some difficulty at first. The material loses shape if boiled, and phenol and alcohol render the surface rough and gummy. Aqueous metaphen solution proved to be satisfactory.

*The Placement of the Drains.*—The most satisfactory use of these drains has been found in osteomyelitis of the tibia, in which it seemed possible to maintain dependent drainage regardless of whether the patient was recumbent or upright. In the first case in which the method was tried, the drains were inserted as illustrated in Fig. 3, and subsequent cases have differed from this only in minor details.

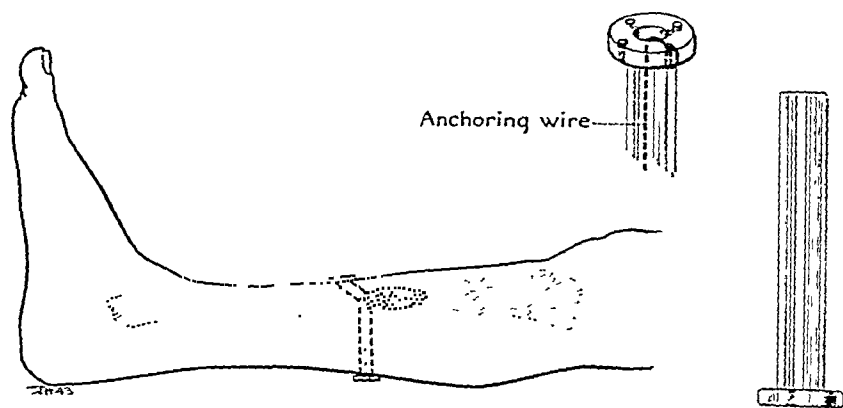


Fig. 3.—The lucite drain. It is 1 cm. in external diameter and 7 mm. internally; it is of varying lengths. There is a flange 18 mm. in diameter at one end, in which holes are drilled. The drains are inserted in such fashion as to allow dependent drainage of osteomyelitic cavities regardless of whether the patient is in the recumbent or the upright position. The flange of the anterior drain is bent to be parallel with the skin. A stainless steel wire passes through both drains and the leg, and is anchored to each flange.

To accomplish proper placement in the tibia, the skin and soft tissues over the anterior surface of that bone were incised, the bone was opened anteriorly into the pocket, and most of the bony roof of the cavity was removed. At the caudal end of the cavity, a  $1\frac{3}{32}$  inch drill was used to penetrate the bone straight back, and the graduated-diameter trocars of Wangensteen's set for drainage of lung abscess<sup>11</sup> were pushed through the soft tissues and skin posteriorly until a large enough trocar had been reached to permit placement of a lucite drain from behind. It was quickly learned that the head of the drain must lie about  $\frac{1}{4}$  mm. away from the skin at first, to prevent pressure irritation from post-operative swelling of the calf muscles. The anterior drain site was exposed by excision of a disc of skin and soft tissue 1 cm. in diameter and a hole for the drain was drilled upward and backward at an angle of about 45 degrees. The head of the anterior drain was placed in hot



A.



B.

C.

Fig. 2.—Reaction of the muscle of a dog adjacent to a piece of lucite left in the tissues for one month. *A*, Layer of fibrosis, rather well vascularized, between site of the plastic material and the muscle layer (magnification  $\times 10$ ). *B*, Junction of the plastic material and muscle, showing fibroblasts, but no inflammatory reaction (magnification  $\times 200$ ). *C*, Surface of the tissue adjacent to the lucite; on the surface are cells suggesting endothelium (magnification  $\times 200$ ).



Roentgenograms in the eighteen months since complete removal of the drains indicate a gradual return toward normal bony architecture (Fig. 7).

*Results of prolonged Drainage in a Series of Patients.*—Twelve lesions in eleven patients have been treated in this fashion. The essential data are presented in Table I. In general, one or two drains were placed in each bone pocket. Apparently complete healing occurred in four of the lesions, frank failure resulted in two, and five are still under treatment. Three of these latter offer definite promise of ultimate success. In one other case the drains have been removed too recently to allow certainty.\*



Fig. 5.—A, Roentgenogram showing marked early destruction of the upper tibia, July 17, 1939, eleven days after onset. B, Progressive sclerosis with formation of a large pocket in the same patient, Jan. 26, 1940.

One of the failures (Case 6) was in disease of the humerus in a fat muscular girl, 11 years of age, in whom the drains could not satisfactorily be held in place; they probably were not properly inserted in the first place. Healing took place later under experimental chemotherapy by Dr. Wesley Spink. In the other failure the disease involved the lower femur, and the bone was of such poor quality that openings for insertion of the drains were made with the thumb nail. The bone has become strong enough to permit use of the leg and all pain has been relieved, but profuse drainage persists after thirty months, and removal of the drain is not tolerated (Case 3).

A striking relief of the discomfort and ache of chronic osteomyelitis has been observed after proper placement of these plastic drains. In

\*Two of these latter cases have healed (5/10/43) since submission of this paper for publication.

water and bent to lie parallel with the skin on insertion. The bone cavity was loosely packed with dry gauze, which was withdrawn during the next few days.

After a trial of a number of methods of securing these drains in place, the use of stainless steel or silver wire was adopted. It is regularly passed through the lumina of both drains, and thus through the extremity, and is anchored to the flange of each drain (Fig. 3). Burial of each end of the wire in one of the holes of the flange prevents catching of the dressings on the ends.

*Use of the Drains in Management of Chronic Osteomyelitis.*—In each case a plaster cast was applied, leaving a wide margin to facilitate change of dressings without contamination (Fig. 4). As soon as healing of the soft tissues had occurred, i.e., in about two weeks, the plaster was removed, and full activity was allowed.

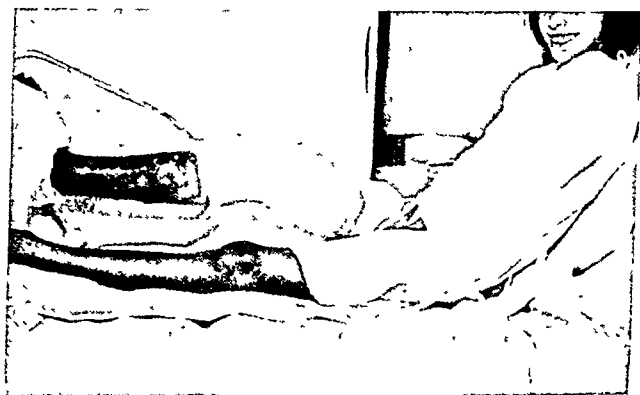


Fig. 4.—The manner of placement of plaster casts for two weeks after insertion of lucite drains. Ample margin is allowed to avoid contamination during irrigations and dressings. There is very little discomfort.

Daily irrigation with Dakin's solution was employed to keep the drains open in most of the cases.

The first patient treated in this manner was a boy of 12 years of age who had had osteomyelitis of the tibia for nine months. The lesion showed little prospect of healing, and a large pocket was visible on roentgen examination in the upper end of the bone (Fig. 5). On Feb. 8, 1940, lucite drains were placed as already described. Subsequent roentgenograms indicated a gradual healing of the pocket, apparently by regeneration of bone (Fig. 6). The drains were both shortened six months after insertion, and again at twelve months; the posterior drain and anchoring wire were completely removed at thirteen months; and finally, the anterior drain, which had been held for three months with adhesive plaster and heavy thread was removed at sixteen months. The drainage sites healed within a few days and have remained healed, allowing the boy to play football at school without apparent handicaps.

Fig. 6.



Fig. 7.

Fig. 6.—*A*, Roentgenograms of the same patient, April 16, 1940, two months after insertion of the drains. Casts were not usually used this long. *B*, Diminution in sclerosis and beginning healing of the bone cavity, Jan. 2, 1941.

Fig. 7.—*A*, Roentgenogram showing continued diminution in sclerosis, and partial healing of the drainage tract on July 31, 1941, two months after removal of the drains. *B*, Plate of same bone as Figs. 5 and 6 showing appearance on Aug. 26, 1942, fifteen months after removal of the drains. The appearance of the bone has returned almost to normal.

TABLE I  
COURSE OF CHRONIC OSTEOMYELITIS FOLLOWING USE OF LUCITE DRAINS

PATIENT NO.	AGE OF PATIENT	DURATION OF DISEASE	SITE	NO. OF DRAINS	DURATION OF DRAINAGE	DATE OF REMOVAL	PRESENT STATUS
1. T. M.	(683797)	12 yr.	tibia	2	16 mo.	6/ 6/41	Healed 18 mo. (1/1/43)
2. G. J.	(609738)	13 yr.	radius	2	1½ mo.	4/ 8/40	Healed 3 mo. (10/16/40)
3. A. H.	(684222)	27 yr.	femur	2	30 mo.		Drain in place, not promising
4. M. V. B.	(699394)	9 yr.	tibia	7	20 mo.		2 drains in place, still promising
5. E. H.	(648299)	32 yr.	tibia	2	15 mo.	8/24/42	Healed 2 mo. (2/1/43)
6. P. M.	(695433)	10 yr.	tibia humerus	1 2	9 mo. 10 mo.	6/26/42 11/27/42	Healed Failure; healed by chemotherapy
7. L. E.	(633500)	11 yr.	tibia	4	13 mo.		2 drains in place
8. F. C.	(714164)	31 yr.	tibia	2	9½ mo.	8/31/42	Healing (?)
9. E. F.	(698881)	22 yr.	tibia	2	12 mo.		Drains in place
10. A. V.	(717558)	30 yr.	femur	9	11 mo.		Drains in place
11. G. B.	(723367)	20 yr.	tibia	2	6 mo.		Drains in place

At the present time, tubes of the type described by Pearse are being placed in the common bile ducts of dogs in order to determine the degree of reaction to them.

With regard to the problem of osteomyelitis, the importance of continuous drainage is thought to rest in the quick evacuation of pus and also in the prevention of local pressure elevation, even though use of a manometer and a hollow drill inserted into foci of recurrent osteomyelitis has failed on two occasions to demonstrate such a rise. This contention is supported by the marked relief of discomfort which is afforded by placement of drains.

The proper time period during which drains should remain in place has not been settled. In Case 8, they were apparently removed too early, and healing after removal does not seem too certain to occur. For the larger bones, it appears at present wisest to shorten or remove drains only when roentgen evidence indicates healing to the end of the drain. In the tibia, this has meant about fifteen months of drainage.

The management of chronic osteomyelitis has been materially altered by the brilliant reports of Spink and Paine, followed later by Dickson, Dively, and Kiene, and by Key. They observed healing in a high percentage of cases following saucerization, sulfathiazole implantation, and primary closure. At the University of Minnesota Hospitals healing has occurred seven times in twelve trials of this method, and in two other cases healing still seems likely to occur. These patients in whom healing has taken place are not immune to occasional bouts of recurrent pain, and their roentgen pictures indicate the persistence of abnormal bony architecture. In my opinion, therefore, long-continued dependent drainage is the form of treatment which best restores normal bony architecture and therefore may best be expected to achieve a permanent cure.

Utilization of this method of therapy seems best adapted to superficial long bones, particularly the tibia. This is the bone in which saucerization, sulfathiazole implantation, and primary closure are most difficult because of the inadequacy of soft tissues for obliteration of the resulting dead space. It is likely that judicious choice between the two methods in specific cases will offer the best over-all results.

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most of the cases, return to normal activity has been demanded by the patient, and no ill effect from this has been recognized (Fig. 8). The patient who now wears nine drains in his femur had been bedridden for a year despite numerous conventional procedures for his disease. After placement of the drains, he walked about the house within two months, and is achieving gradually increasing activity.

In Table I, the patient in Case 2 had sodium sulfathiazole irrigations for three days through the drains, and the patient in Case 10 had local implantation of 8 Gm. of free sulfathiazole at the time of placement of the drains. Aside from these two, no local chemotherapeutic agent except Dakin's solution has been employed, the aim being to evaluate continued drainage before the admixture of other measures.

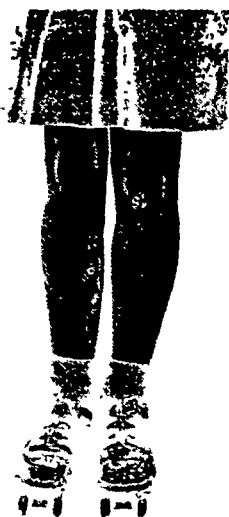


Fig. 8.—A patient who has worn drains for a year, and has had some of them removed. Most patients demand full activity within a few weeks after insertion of lucite drains.

#### COMMENT

Lucite, being relatively little irritating to the tissues, has been implanted elsewhere in the body. W. T. Peyton, of this clinic, has implanted a lucite orbital roof in a patient at my suggestion, and the plate is still in place after over six uneventful months. Serious consideration is being given to the preparation of larger plates to use in covering defects in the skull. Such plastic plates would have an advantage over vitallium because of the pliability of the material under hot water.

Lucite is also being used in experimental work by K. A. A. Merendino, in the laboratory, where it has been found most useful to make cannulae of practical design for gastric pouches during further study of the ulcer problem.

## RADICAL OPERATION FOR INTRACTABLE PRURITUS ANI

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**P**RURITUS ani is a symptom complex rather than a definite disease, characterized by intense itching about the anus. The itching is aggravated by warmth and hence is often most troublesome at night.

There probably is no single cause of this symptom. In adults it is most often associated with moist perianal skin. The moisture in women may be due to chronic vaginal discharge, and in both men and women to irritative rectal lesions such as fissure or hemorrhoids. Moist perianal skin is more common in obese individuals, due to constant apposition of the buttocks. In some patients infrequent bathing may be a contributory factor. The symptom is frequent in diabetics.

In most instances of long continued pruritus ani, the perianal skin becomes pigmented, leathery, thickened, and often excoriated by scratching. These changes may be due to a disease entity, but more probably are the end results of repeated injury from scratching. A microscopic examination of this scarred pigmented perianal skin shows nothing other than increased deposits of pigment and chronic inflammation.

In many instances the symptoms may be relieved by the correction of local anal lesions; in others, by scrupulous cleanliness and the use of drying ointments or powders. In all cases these general causes should be looked for and, if present, treated.

In more refractory cases subcutaneous alcohol injections have been used to destroy nerve endings in the perianal area. This treatment is based on the same rationale as the older surgical procedure of undercutting the perianal skin and subcutaneous tissues and then suturing the flaps so raised in their original beds.

We are all familiar with the above facts but we are also well aware that there are occasional stubborn cases of pruritus ani which are not relieved by any of these measures. Hence, any method of treatment which affords relief from the intractable itching occasionally encountered should receive attention.

It should not be inferred that the radical method reported here should be used in all, or even an appreciable percentage, of cases of pruritus ani but in the occasional instance where symptoms are severe and cannot be relieved by ordinary methods. The following report is of such a case.

Presented at the meeting of the Society of University Surgeons, Chicago, Ill., Feb. 11-13, 1943.

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about one year after operation she said that she had difficulty sitting for prolonged periods. This was due not to soreness but a feeling about the anus of numbness similar to when one's leg "goes to sleep." At the end of about a year sensation returned to the shifted skin and she no longer had this difficulty. On examination the skin appeared perfectly normal with good sensation. The result was considered excellent.

#### OPERATIVE TECHNIQUE

Because of the probability of some infection and perhaps consequent poor and prolonged healing, we believe it best to excise only one-half the involved perianal skin at a time. This allows a safety factor, in case infection and scarring might cause contracture of the anal orifice. The procedure in brief is a complete excision of the scarred perianal skin, one hemisphere at a time, and a shift of a flap from the medial surface of the buttock and thigh to replace the excised area. The flap need not be delayed because the blood supply is entirely adequate.

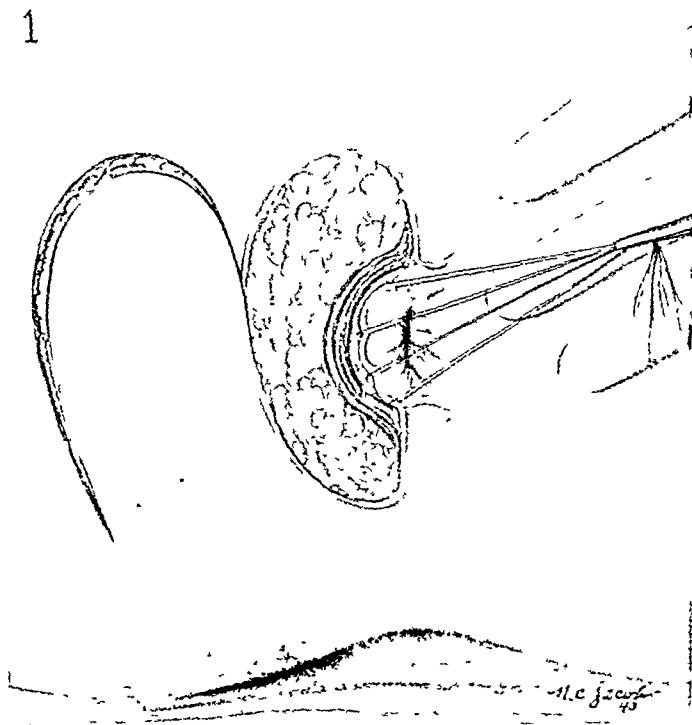


Fig. 1.—Showing the manner in which the flap is cut for resurfacing one-half the perianal area

An incision is made at the mucocutaneous junction around one-half the circumference of the anus. The mucosal edge is prevented from retracting inward by a number of guy sutures which are held by an assistant. The external sphincter muscle is exposed and the scarred skin and subcutaneous tissues dissected from it. A plane of dissection is

## CASE REPORT

M. S. (S.M.H. No. 146602), a white physician's wife, aged 51 years, entered the Strong Memorial Hospital on Jan. 3, 1939. She complained of pruritus vulvae. This symptom, at times more troublesome than at others, had been experienced for the past twenty years. In the past one or two years it had become more severe and the itching had extended to the perianal region. Leucorrheal discharge, which had always been present, had become quite marked in the past year. This did not seem to have aggravated the itching. Her last menstrual period had been in January, 1938. During the two years prior to entry she had been treated with both radium and x-ray radiation over the vulvar and anal regions. The exact dosage was unknown, but there had been no relief of symptoms. During the three months before hospital admission she had received 10,000 units of progynon a week, for six weeks, without improvement. During the month before admission she had been given 10,000 units of progesterone twice a week. This had given slight relief from itching.

A detailed history revealed nothing of importance in the past, other than that she had always been in good health. A cholecystectomy and appendectomy had been done twelve years previously.

General physical examination showed no abnormal findings. The labia majora and minora were hypertrophied, thickened, red, and scaly. This abnormal condition extended up to the mons and downward around the anus. Rectal examination showed hemorrhoids present externally.

Laboratory findings were Hb., 14.5 Gm.; R.B.C., 4,750,000; W.B.C., 6,000; blood N.P.N., 35 mg. per cent; blood sugar, 145 mg. per cent; urine, negative; Wassermann, negative.

The diagnosis made on the gynecological service where she was first admitted was kraurosis vulvae and pruritus vulvae.

On Jan. 4, 1939, a radical vulvectomy, a dilatation and curettage, and a cauterization of the cervix was done on the gynecological service. At the same time the external hemorrhoids were removed. She had a satisfactory convalescence and was discharged on Jan. 28, 1939, with the vulvar incisions healed.

This operation relieved her entirely of pruritus vulvae but not of pruritus ani. On March 28, 1939, we were asked to see her because of the intense anal itching. At that time there was an area from the vaginal orifice to the tip of the coccyx and extending laterally about the anus for about two inches which was thickened, red, and leathery, with some white plaques interspersed through the red area. Since vulvectomy there had been no leucorrhea and an attempt had been made to control the itching by keeping the skin dry with borated alcohol. This had not been at all effective in controlling the itching.

She was advised to have the involved perianal skin excised. She entered the hospital again and on April 25, 1939, the right half of the pruritic area was excised and the defect covered with a flap. During the postoperative period the main problem was one of keeping the area dry. She was kept on her stomach to prevent vaginal discharge and urine from running down over the wound. The bowels were allowed to move on the ninth postoperative day. The flap healed in place well and she was discharged on the fourteenth postoperative day. At that time there was a small granulating area laterally from which the flap had been shifted. This healed promptly.

On July 6, 1939, as the right side was symptomless and had been healed for some time, the remaining left hemisphere of scarred perianal tissue was excised and covered with a flap. It was possible on this side to close the defect from which the flap was obtained. These wounds healed nicely so that she could be discharged from the hospital on July 24.

She was last seen on May 16, 1941, a little less than two years after completion of the two-stage operation. At that time she was entirely free from itching. For

long enough periods to be thought permanently relieved. The third has had one hemisphere of perianal tissue removed and is about to have the operation completed. As yet he still has marked symptoms on the unoperated side. He also complains of itching on the flap on the operated side although this skin is still anesthetic. Whether this is actual or due to the unoperated side will be determined on completion of the procedure.

It would seem that in a selected group of cases of pruritus ani, where all other measures have proved ineffectual in relieving symptoms, that complete excision of the abnormal perianal tissues, one-half at a time, and replacement with a flap from the buttock and thigh may be effective treatment.

found under the leathery area and the dissection carried outward from normal skin. The flap of scarred tissues is then cut away (Fig. 1). A flap of skin and subcutaneous tissue of correct size and shape to cover the defect is cut lateral to the defect with its base posteriorly. It is swung across and sutured to the anal mucosa and to the medial line of excision (Fig. 2). The defect left laterally is sutured as far as possible. If tension is observed, the remainder of the defect is left to granulate. The operation is done in the lithotomy position and any tension on the flap becomes less

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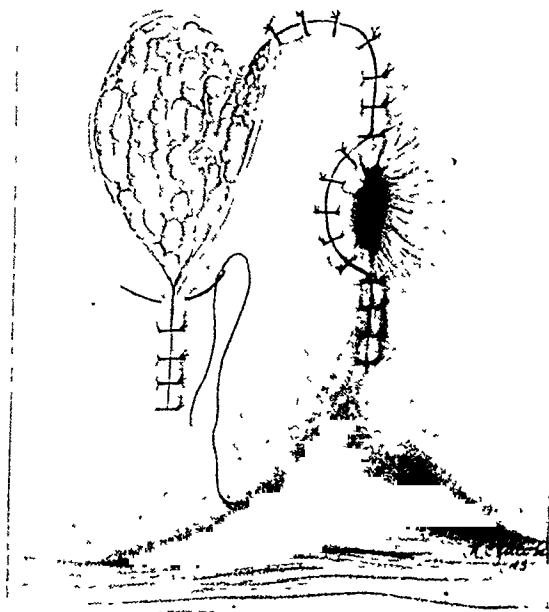


Fig. 2.—The flap has been sutured medially and the closure of the lateral defect begun. It is usually possible to close this incision, but if there is any tension, the superior portion is allowed to granulate.

when the legs are again straight. A small rubber drain is brought out from under the flap at its base and a snug perineal binder is applied to hold the flap securely in apposition to its bed. The bowel is prevented from moving for ten to fourteen days depending upon the speed of healing. Infection is moderate. There is usually some inflammatory reaction along the suture lines but not enough to interfere with healing. In two to three months the remaining half of the perianal skin is removed and replaced in the same manner.

#### DISCUSSION

We have so far had occasion to operate on three such patients with intractable pruritus ani. Two of these are entirely symptom free for

## MATERIAL AND METHODS

This study is based upon the findings of eighty-eight patients who have had gastric resections for peptic ulcer, of which twenty-five were gastric and sixty-three duodenal. The follow-up studies and gastric analyses were performed repeatedly over a period of from one to seven years after operation; however, only 25 per cent were followed for more than five years. All patients were personally interrogated, and rather severe criteria were used as a basis for evaluating results. Likewise all analyses were performed by us and on some patients as many as six gastric analyses were done. All patients listed as having low acid or anacidity had at least two determinations done. Additional patients studied, in whom it was felt that satisfactory tests were not obtained, are not included in this report.

The method used in obtaining specimens of gastric juice is that suggested by Bloomfield and Pollard.<sup>9</sup> The examination is made after a fast of twelve hours, with histamine used as a stimulus in a dosage of 0.1 mg. to each 10 kg. of body weight. The fasting contents are withdrawn, the histamine injected subcutaneously, and the stomach contents continuously aspirated with a syringe and collected for three ten-minute periods. The acidity is then titrated against  $\frac{1}{10}$  normal sodium hydroxide, Toepfer's reagent and phenolphthalein being used as indicators. The ten-minute specimen with the greatest ten-minute volume of secretion and the highest titratable acidity obtained is considered the index of gastric function. The importance of following the described procedure in detail in order to obtain an accurate analysis cannot be too greatly stressed.

To insure a precise determination of acid secretion, several requisites must be recognized. First, the person performing the aspiration must be a physician familiar with the technique of gastric aspiration and must be interested in the procedure. The delegation of the test to a nurse or to a technician repeatedly leads to error. It has been our experience on numerous occasions that the results obtained by the relatively uninterested technician will not compare with the results obtained by a doctor who is responsible for and interested in the result obtained. Second, the stomach must be aspirated absolutely dry before the fractional specimens are collected. This procedure frequently takes from ten to fifteen minutes and on occasions the test may have to be abandoned for the day because of the constant regurgitation of bile. Third, dilution of the gastric contents must be avoided; the patient should be required to expectorate all saliva and all bile-tinged specimens should be discarded. The volume of secretion characteristically follows a more or less regular curve and this characteristic can also be used to check the accuracy of the procedure. Fourth, there are obvious difficulties and inaccuracies in these determinations on the postoperative stomach, and for this reason repeated studies must be made on those patients who are found to have low acid or anacidity. Since the error in gastric analyses

## GASTRIC ACIDITY FOLLOWING GASTRIC RESECTION

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**D**URING the past twenty years gastric resection has become more and more popular as a method of surgical treatment of peptic ulcer. There are two advantages of this procedure over the more conservative operations such as pyloroplasty or gastrojejunostomy. They are, first, that the ulcer is removed and, second, that the gastric acidity may be lowered, thereby reducing the danger of the development of secondary ulcer. It is now realized that small resections usually fail to reduce the acidity and, as a result, larger resections as well as various mutilating procedures on the stomach have been advised in the hope of regularly producing postoperative gastric anacidity.

The purposes of this report are to present a summary of findings on eighty-eight patients upon whom gastric resections have been performed for peptic ulcer and to emphasize certain technical features of resection which make it a practical procedure and one often resulting in a low postoperative acidity.\*

There are many surgeons<sup>1-6</sup> who advocate extensive resections of the stomach in the hope of insuring a low postoperative acidity. Their opinion is based upon the generally accepted idea that gastric acidity plays an important part in either the formation or the persistence of an ulcer and that if postoperative anacidity can be obtained, secondary or recurrent ulcer can be prevented. The objections to these extensive resections (more than two-thirds of the stomach) are, first, that it has not been proved to date that they are more effective in reducing acidity than less extensive resections (one-half to two-thirds). Second, when such a large amount of stomach is sacrificed and a recurrent ulcer develops, a secondary procedure is not only difficult but hazardous; and third, except in the hands of an expert, the mortality is too high. With these features in mind, we have attempted to determine the type of resection that most often produces a low postoperative acidity, is relatively safe and simple, and also retains a sufficient amount of stomach in case a secondary operation becomes necessary.

\*A detailed analysis of all cases of peptic ulcer operated upon in the New York Hospital is being reported by Heuer et al.<sup>7</sup>

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curvature is left in situ, then this procedure would best serve not only to secure reduction of acidity but also to retain resection as a practical technical procedure. In addition, this type of resection would be possible for a large number of surgeons to perform and also, if marginal ulcer should develop, would allow secondary resection to be carried out without too great a hazard. The increasing number of reports showing that marginal ulcer occurs in from 5 to 10 per cent of all cases following gastric resection emphasizes the wisdom of not removing too much stomach at the time of the primary resection. One way to accomplish this is to retain a large portion of the greater curvature. Our studies not only confirm the thesis that removal of the lesser curvature does considerably lower the acidity but also show that retaining a fair portion of the greater curvature does not appreciably alter the result (Table II).

TABLE II  
RESECTION  $\frac{1}{2}$  TO  $\frac{2}{3}$  OF STOMACH INCLUDING INCISURA ANGULARIS

	NUMBER	ANACIDITY	LOW ACIDITY	NORMAL OR ADEQUATE ACIDITY*
Gastric ulcer	12	9	3	0
Duodenal ulcer	34	16	9	9
	46	25 (54%)	12 (26%)	9 (20%)

\*Free hydrochloric acid of 60 degrees or more was considered normal or adequate acid.

Other papers<sup>6, 10-15</sup> may be consulted for a review of the present concepts concerning the physiology of the stomach, but suffice it to say here that up to the present time there has been no adequate explanation for the anacidity that frequently follows subtotal gastric resection. Furthermore, a tremendous amount of experimental work has been done without solving the problem. It is even more difficult to explain why gastric resections that include the lesser curvature above the incisura angularis but that leave one-half to two-thirds of the greater curvature should result in anacidity in almost as high a percentage of cases as do resections of considerably larger portions of stomach.

Studies on the last group of cases (Fig. 1, C) i.e., those in which more than two-thirds of the stomach was removed, reveal that approximately 90 per cent of the cases show low or absent acidity, only 10 per cent better than the preceding group (Table III).

TABLE III  
RESECTION OF MORE THAN  $\frac{2}{3}$  OF STOMACH

	NUMBER	ANACIDITY	LOW ACIDITY	NORMAL OR ADEQUATE ACIDITY*
Gastric ulcer	7	7	0	0
Duodenal ulcer	4	1	2	1
	11	8 (73%)	2 (18%)	1 (9%)

\*Free hydrochloric acid of 60 degrees or more was considered normal or adequate acid.

results in too low rather than too high a value of secretion, it is not uncommon to discover that a patient in whom a previous anacidity was found, upon repeated test, shows adequate acid.

The normal standard of gastric secretion as obtained by the method just described has been determined by Bloomfield and Pollard.<sup>9</sup> In general, it may be said that the normal range of free hydrochloric acid is between 60 and 110 degrees and the maximum ten-minute secretory volume between 15 and 35 c.c.

### RESULTS

The types of resection may be divided into three groups: (1) those in which the antrum was removed (Fig. 1, *A*); (2) those in which one-half to two-thirds of the stomach and a portion of the lesser curvature beyond the incisura angularis were removed (Fig. 1, *B*), and (3) those in which more than two-thirds of the stomach was removed (Fig. 1, *C*). Several observers have reported that simple removal of the antrum of the stomach usually fails to reduce the postoperative acidity; our observations confirm these reports (Table I). Our main point of interest was

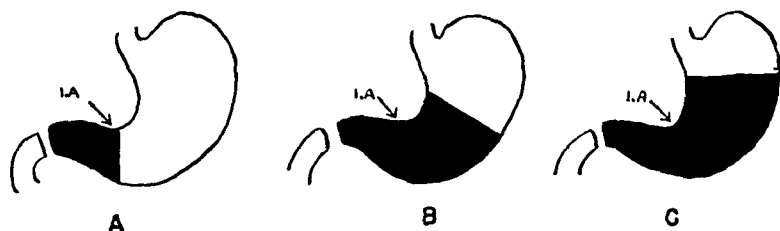


Fig. 1.—Three types of resection which were done upon patients discussed in this report. *A*, Resection of pyloric antrum; *B*, Resection as we suggest, carried proximal to the incisura angularis (*I.A.*) on lesser curvature and leaving a fair portion of the greater curvature; *C*, resection of more than two-thirds of the stomach.

to determine whether removal of one-half to two-thirds of the stomach as shown in Fig. 1, *B* results in as high a percentage of anacidity as does removal of larger portions of the stomach (more than two-thirds, Fig. 1, *C*).

TABLE I  
ANTRAL RESECTION

	NUMBER	ANACIDITY	LOW ACIDITY	NORMAL OR ADEQUATE ACIDITY*
Gastric ulcer	6	2	2	2
Duodenal ulcer	25	0	4	21
	31	2 (6%)	6 (19%)	23 (75%)
		25%		

\*Free hydrochloric acid of 60 degrees or more was considered normal or adequate acid.

It has been suggested that in performing gastric resection the site of division should be carried proximal to the incisura angularis (*I.A.* in Fig. 1) to insure low postoperative acidity. If such a resection decreases acidity while at the same time a large portion of the greater



curvature is left in situ, then this procedure would best serve not only to secure reduction of acidity but also to retain resection as a practical technical procedure. In addition, this type of resection would be possible for a large number of surgeons to perform and also, if marginal ulcer should develop, would allow secondary resection to be carried out without too great a hazard. The increasing number of reports showing that marginal ulcer occurs in from 5 to 10 per cent of all cases following gastric resection emphasizes the wisdom of not removing too much stomach at the time of the primary resection. One way to accomplish this is to retain a large portion of the greater curvature. Our studies not only confirm the thesis that removal of the lesser curvature does considerably lower the acidity but also show that retaining a fair portion of the greater curvature does not appreciably alter the result (Table II).

TABLE II

RESECTION  $\frac{1}{2}$  TO  $\frac{2}{3}$  OF STOMACH INCLUDING INCISURA ANGULARIS

	NUMBER	ANACIDITY	LOW ACIDITY	NORMAL OR ADEQUATE ACIDITY*
Gastric ulcer	12	9	3	0
Duodenal ulcer	34	16	9	9
	46	25 (54%)	12 (26%)	9 (20%)
			80%	

\*Free hydrochloric acid of 60 degrees or more was considered normal or adequate acid.

Other papers<sup>6, 10-15</sup> may be consulted for a review of the present concepts concerning the physiology of the stomach, but suffice it to say here that up to the present time there has been no adequate explanation for the anacidity that frequently follows subtotal gastric resection. Furthermore, a tremendous amount of experimental work has been done without solving the problem. It is even more difficult to explain why gastric resections that include the lesser curvature above the incisura angularis but that leave one-half to two-thirds of the greater curvature should result in anacidity in almost as high a percentage of cases as do resections of considerably larger portions of stomach.

Studies on the last group of cases (Fig. 1, C) i.e., those in which more than two-thirds of the stomach was removed, reveal that approximately 90 per cent of the cases show low or absent acidity, only 10 per cent better than the preceding group (Table III).

TABLE III

RESECTION OF MORE THAN  $\frac{2}{3}$  OF STOMACH

	NUMBER	ANACIDITY	LOW ACIDITY	NORMAL OR ADEQUATE ACIDITY*
Gastric ulcer	7	7	0	0
Duodenal ulcer	4	1	2	1
	11	8 (73%)	2 (18%)	1 (9%)
			91%	

\*Free hydrochloric acid of 60 degrees or more was considered normal or adequate acid.

Our findings show that, although the acidity is affected by the type of resection performed, the results are not so affected and bear little relationship to the postoperative acidity (Tables IV, V, VI, and VII). However, as the postoperative period of time increases, the chances are that more marginal ulcers will develop in those patients who had duodenal ulcer. Furthermore, it is likely that these will occur most often in those patients who have adequate postoperative acidity since, up to the present time, all marginal ulcers observed in this clinic occurred in patients with adequate acidity.

TABLE IV  
RESULTS OF RESECTION IN RELATION TO ACIDITY

	NUMBER	PER CENT	SATISFACTORY NUMBER PER CENT	UNSATISFACTORY NUMBER PER CENT
<i>Gastric Ulcer (25)</i>				
Low or anacidity	23	92.	22 96.	1 4.
Adequate (normal)	2	8.	2 100.	0 0.
<i>Duodenal Ulcer (63)</i>				
Low or anacidity	32	50.	30 94.	2 6.
Adequate (normal)	31	50.	26 84.	5* 16.
<i>All Cases (88)</i>				
Low or anacidity	55	63.	52 95.	3 5.
Adequate (normal)	33	37.	28 85.	5* 15.

\*One died.

TABLE V  
CLINICAL RESULTS IN RELATION TO TYPE OF RESECTION

	NUMBER	SATISFACTORY	UNSATISFACTORY
<i>Antral Resection</i>			
Gastric ulcer	6	6	0
Duodenal ulcer	25	21	4 (one died)
<i>Resection of <math>\frac{1}{2}</math> to <math>\frac{2}{3}</math> of Stomach Including Incisura Angularis</i>			
Gastric ulcer	12	11	1
Duodenal ulcer	34	29	5
<i>Resection of More Than <math>\frac{2}{3}</math> of Stomach</i>			
Gastric ulcer	7	7	0
Duodenal ulcer	4	4	0

TABLE VI  
CLINICAL RESULTS IN RELATION TO ACIDITY AND TYPE OF RESECTION

	PER CENT WITH LOW OR ANACIDITY	PER CENT WITH SATISFACTORY RESULTS
<i>Antral Resection</i>		
Gastric ulcer	66.	100.
Duodenal ulcer	16.	81.
<i>Resection of <math>\frac{1}{2}</math> to <math>\frac{2}{3}</math> of Stomach Including Incisura Angularis</i>		
Gastric ulcer	100.	91.
Duodenal ulcer	74.	85.
<i>Resection of More Than <math>\frac{2}{3}</math> of Stomach</i>		
Gastric ulcer	100.	100.
Duodenal ulcer	75.	100.

TABLE VII

PRE- AND POSTOPERATIVE ACIDITY AND CLINICAL RESULTS IN CASES OF GASTRIC AND DUODENAL ULCER FOLLOWING THE THREE TYPES OF RESECTION DESCRIBED

NUMBER	AGE	PREOPERATIVE ANALYSIS*			POSTOPERATIVE ANALYSIS	AMOUNT RESECTED†	RESULT		
		V	F	T					
GASTRIC ULCER									
<i>Patients With Postoperative Anacidity</i>									
1.	47	55	60	75	Anacidity	2	E		
2.	32	80	68	76	Anacidity	3	E		
3.	38	7	75	100	Anacidity	2	E		
4.	58	25	68	83	Anacidity	3	G		
5.		42	90	100	Anacidity	2	E		
6.	62	60	70	80	Anacidity	2	E		
7.	65	?	102	124	Anacidity	2	G		
8.	61	60	85	96	Anacidity	3	E		
9.	52	52	57	81	Anacidity	2	E		
10.	43				Anacidity	2	E		
11.	54				Anacidity	1	E		
12.	48				Anacidity	3	E		
13.	59				Anacidity	3	E		
14.	49				Anacidity	3	E		
15.	45				Anacidity	2	E		
16.	46				Anacidity	1	E		
17.	42				Anacidity	3	G		
18.	55				Anacidity	2	G		
<i>Patients With Low Postoperative Acidity</i>									
					V	F	T		
1.	51	64	64	76	30	50	75	2	E
2.	59	110	83	92	20	45	50	1	E
3.	46	55	94	105	5	14	50	2	F
4.	53	150	59	62	12	40	48	2	E
5.	42				7	44	64	1	E
<i>Patients With Adequate (Normal) Postoperative Acidity</i>									
1.	50	50	96	106	25	111	121	1	G
2.	37	45	90	115	15	98	106	1	G
DUODENAL ULCER									
<i>Patients With Postoperative Anacidity</i>									
1.	47	120	112	130	Anacidity	2	E		
2.	52	30	91	107	Anacidity	2	E		
3.	52	50	100	107	Anacidity	2	E		
4.	54	?	104	145	Anacidity	2	E		
5.	45	60	95	110	Anacidity	2	E		
6.	48	45	61	79	Anacidity	2	E		
7.	52	7	95	105	Anacidity	2	E		
8.	57	45	104	120	Anacidity	2	E		
9.	50	30	58	70	Anacidity	2	E		
10.	40	7	90	100	Anacidity	2	E		
11.	24	50	70	85	Anacidity	2	E		
12.	52	?	70	85	Anacidity	2	P		
13.	52	30	80	138	Anacidity	2	F		
14.	44	46	64	74	Anacidity	2	E		
15.	54				Anacidity	3	E		
16.	35				Anacidity	2	E		
17.	38				Anacidity	2	F		

\*V. Volume  
F. Free acid  
T. Total acid

†1. Antrectomy  
2. Removal of  $\frac{1}{2}$  to  $\frac{2}{3}$ , including incisura angularis  
3. Removal of more than  $\frac{2}{3}$  of stomach

TABLE VII—CONT'D

NUMBER	AGE	PREOPERATIVE ANALYSIS*			POSTOPERATIVE ANALYSIS			AMOUNT RESECTED†	RESULT
		V	F	T	V	F	T		
Patients With Postoperative Low Acidity									
1.	41	?	90	92	10	30	33	3	G
2.		50	75	90	12	44	54	2	E
3.	43	21	69	84	10	53	55	2	G
4.	42	21	85	108				1	G
5.	56	100	96	104	6	38	64	2	E
6.	25	50	104	109	8	54	77	3	G
7.	32	?	74	86	15	40	50	2	E
8.	45	20	84	95	5	32	42	2	G
9.	40	30	95	105	20	40	52	2	G
10.	52	81	108	116	15	15	22	2	E
11.	53				15	40	50	1	E
12.	46				7	42	50	1	G
13.	35				37	17	32	2	E
14.	41				10	45	65	2	G
15.	48				25	15	25	2	E
Patients With Adequate (Normal) Postoperative Acidity									
1.	42	250	69	85	40	95	104	1	E
2.	30	56	69	83	60	79	90	2	P
3.	32	45	94	104	30	63	75	1	G
4.	41	75	114	122	35	78	85	1	G
5.	51	30	98	106	30	104	110	1	E
6.	29	?	59	68	50	95	110	1	G
7.	40	35	70	91	20	64	82	1	G
8.	39	92	102	118	115	100	108	3	G
9.	23	20	86	94	17	98	120	2	G
10.	51	7	72	88	40	130	135	2	E
11.	52	?	110	119	25	93	112	2	E
12.	23	23	84	85	40	90	96	1	G
13.	41	7	93	103	30	95	109	1	E
14.	46	90	94	110	40	87	97	1	E
15.	56	29	99	104	18	100	108	1	E
16.	36	55	85	96	20	88	92	1	E
17.	45	105	134	144	95	97	120	2	E
18.	31	45	95	108	35	88	91	1	P
19.	36	65	127	134	65	127	124	2	E
20.	46	30	90	104	22	74	91	2	G
21.	48	?	81	88	35	105	112	1	G
22.	51	?	119	125	20	93	97	1	E
23.	72				70	89	105	1	Died
24.	42				17	80	85	1	P
25.	51				40	70	78	2	P
26.	54				35	93	96	2	E
27.	50				35	90	108	1	E
28.	57				30	70	75	1	E
29.	32				30	90	110	1	G
30.	37				15	95	100	1	G
31.	52				40	60	72	1	G

## CONCLUSIONS

In reviewing the results of these three types of resection, we find that removal of the antrum results in reduced acidity or anacidity in only 25 per cent of the patients. Removal of one-half to two-thirds of the stomach plus a portion of the lesser curvature proximal to the resultant angle results in 80 per cent of the patients having reduced acidity or

anacidity. Removal of more than two-thirds of the stomach results in 90 per cent of the patients having reduced acidity or anacidity. As previously stated, many advantages in technique are sacrificed when large portions of the stomach are removed, and it seems from our results that little is gained. To retain resection as a useful procedure, we advise that gastric resection be done in such a manner as to insure the highest percentage of cases of postoperative anacidity without sacrificing too much of the stomach. This can be done by removing one-half to two-thirds of the stomach, including a portion of the lesser curvature proximal to the re-entrant angle, and retaining a fair portion of the greater curvature.

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# ACUTE ABDOMINAL SYMPTOMS IN ARACHNIDISM

## BLACK WIDOW SPIDER BITE

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THE syndrome produced by the bite of the black widow spider (*Lactrodectus mactans*), when duly recognized, is not a surgical problem. However, because of the abdominal symptoms usually resulting from arachnidism and the fact that the patient often attaches little or no significance to the spider bite, it behooves all surgeons to be familiar with the clinical picture of this condition if needless operations are to be avoided. Morton,<sup>17</sup> in a careful study of the cases observed at the University of Virginia Hospital, stated that "The most outstanding symptom in each case was the severe and usually cramplike abdominal pain; while the most important physical abnormality was the extreme boardlike rigidity of the abdominal musculature." Noland<sup>19</sup> emphasizes that patients with arachnidism are often sent to a hospital by the referring doctor with a diagnosis of some acute surgical condition of the abdomen. Patients suffering from arachnidism are occasionally subjected to celiotomy. It appears from the recent reports of D'Amour and his associates,<sup>10, 11</sup> Kirby-Smith,<sup>16</sup> and Frank<sup>21</sup> that the incidence of arachnidism is increasing. In spite of these facts the subject has received very little attention in the surgical literature.

### THE SPIDER

*Lactrodectus mactans* is a common spider which may be found throughout the United States and in Canada.<sup>15, 16</sup> This spider may be found in woods and fields but is also not infrequently seen about protected areas such as garages, basements, and outhouses. The reason more individuals are not bitten is due more to the characteristics of the spider than to any lack of its presence in various localities. The black widow spider is a timid creature and seldom bites a human being except when crushed or contacted in the dark. If the web of this spider is disturbed, usually the creature retreats and shows little inclination to bite. In turning over old planks, logs, or rocks, individuals may make sudden contact with the spider and be bitten. Many people have been bitten in outdoor privies where in the dark the individual came in contact with the spider.

The *Lactrodectus mactans* female which is the poisonous member of the species may be identified by its black color and bright red hour-glass marking on the ventral surface. The abdomen of the female is

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larger than the male. D'Amour and co-workers<sup>10</sup> and Blair<sup>6</sup> give good descriptions of the life cycle and characteristics of the black widow spider. It has been reported by D'Amour and co-workers<sup>10</sup> that the dried black widow venom is, weight for weight, fifteen times as poisonous as is rattlesnake venom. The dried residue from the venom of one spider weighs .064 mg. The toxic principle of the venom is a protein, probably an albumin. Hall<sup>13</sup> states that the toxin is a nonhemolytic neurotoxin which apparently exerts its effects on nerves and nerve endings.

#### SYMPTOMS OF ARACHNIDISM

The pain produced by the bite is often described as resembling the pain from a pinprick or a small splinter. Frequently patients may pay little or no attention to the bite and may not give the incident in reciting the history of their illness unless specifically questioned. The local lesion may appear as a small red pin-point area or may be invisible. Usually in from one-half to two hours the individual complains of cramping pains which have their origin in the muscle groups near the location of the bite. When bitten on a lower extremity or the genitalia the cramps are first noted in the thighs and hips. In a short time the pain is apt to spread to the abdomen and to be excruciating in intensity. Patients with this condition often appear to have pain comparable in severity to that caused by renal colic, perforated ulcer, or coronary occlusion. A careful history may be difficult to obtain because of the severity of the pain. Further questioning usually reveals severe pain in the thighs, back, and lower chest as well as in the abdomen. The abdominal examination shows the presence of boardlike rigidity although the abdomen usually moves with respiration.<sup>2, 5</sup> Also, there is less tenderness than one would expect to be present in peritonitis producing such marked rigidity. The temperature is apt to be normal when the patient is first seen but fever is likely to develop a few hours later, usually being about 100° F., although occasionally patients have temperature of 101 or 102° F. There may be nausea and vomiting but these symptoms occur less frequently than might be expected in patients exhibiting such marked abdominal rigidity. Leucocytosis of a moderate degree is usually present.

#### TREATMENT

The great majority of patients recover completely from arachnidism in from one to three days with conservative measures regardless of the particular form of therapy used. The large variety of remedies which have been recommended speaks for the inefficiency of most of the agents in producing relief. Morphine sulfate in doses of  $\frac{1}{4}$  and  $\frac{1}{2}$  gr. for an adult frequently gives only partial relief of pain. Magnesium sulfate has often been used intramuscularly in patients with arachnidism with but little evidence of improvement. Intravenous calcium gluconate is recommended by many but exerts relatively little effect on the patient's

general condition. Spinal puncture also has been used without evidence of definite improvement. Frequent hot baths have been found to be a real help in making these patients comfortable.

Specific *Lactrodectus mactans* antiserum when used relatively soon after the bite has been received, now seems to offer the best opportunity for reducing the morbidity of the condition and of making the patient comfortable. Noon and Minear<sup>18</sup> reported spectacular improvement in six patients receiving specific antiserum when given relatively soon after the bite. Kirby-Smith<sup>22</sup> has also observed marked improvement following the use of specific antiserum in several patients in which it has been used since his report published in February, 1942. Specific antiserum gave relief of pain and subsidence of abdominal rigidity in four children reported in Table I. No beneficial results were observed in one adult that received antiserum. The animal experiments of Hall<sup>13</sup> using specific antiserum, support the clinical observations that to be efficacious the antiserum must be used early. Bogen<sup>8</sup> reported "encouraging results" from the use of human immune serum. However, D'Amour<sup>11</sup> showed experimentally that human immune serum is far less potent than the specifically prepared antiserum.

#### END RESULTS

As stated above, the great majority of patients with arachnidism recover without sequelae in from one to three days. The mortality rate of 6.6 per cent as given by Bogen and frequently quoted in the literature appears to be erroneous. These deaths were not collected from established reports in the literature but were collected from newspaper articles, death certificates, and personal communications.<sup>9</sup> Kirby-Smith reports no deaths among 284 cases collected from the literature by various authors.<sup>16</sup>

Fatalities do occur, although they must be relatively unusual. Noon and Minear<sup>18</sup> and Kirby-Smith<sup>16</sup> each report one fatal case. Beasley<sup>4</sup> recently reported a death ascribed to arachnidism and gave the autopsy findings in the case.

#### COMMENT ON TABLE I

The fifty-six cases reported in Table I were seen in the John Gaston Hospital, Memphis, Tenn., between 1933 and 1942 inclusive. The clinical picture presented by this group of patients was essentially that which has been outlined above. Twenty-five of the patients were bitten on either the buttocks or the genitals. Severe abdominal pain was the most important symptom and boardlike rigidity was usually found to be present on abdominal examination. Occasionally patients showed normal temperature charts. The patients in thirty-one of the fifty-six cases studied had a maximum temperature of 99 to 100° F., while nine developed fever of 101° F. or above. Five patients had nausea and vomiting. Leucocytosis was usually present. No significant changes were found on examination of blood pressure, spinal fluid, or urine.



TABLE I  
BLACK WIDOW SPIDER BITE

NO.	AGE	SEX	MONTH	BODY LOCATION	TIME SYMPTOMS DEVELOPED	MAXIMUM TEMPERATURE (DEGREES F.)	W.B.C.	SYMPTOMS
1	30	M	Oct.	Penis	½ hr.	99.8	7,500	evere pain in thigh and chest; mild abdominal pain
2	24	M	Nov.	Ring finger	15 min.	99.0	6,600	Nausea, vomiting, pain in arm, back, and abdomen; abdominal rigidity +++
3	27	M	July		½ hr.	99.0	7,200	Inguinal, abdominal cramps; abdominal rigidity ++++
4	45	M	Aug.	Penis	10 min.	100.0	7,150	Pain in abdomen, generalized aching; slight abdom- inal rigidity
5	34	M	Sept.	Penis	20 min.	99.0	9,900	Inguinal, abdominal cramps, backache, and abdominal rigidity
6	16	M	Sept.	Penis	Not known	101.0	11,760	Nausea, backache, and slight abdominal rigidity
7	40	M	Sept.	Penis	15 min.	99.4	18,500	Vomited 3 times, pain in thighs and abdomen; ab- dominal rigidity ++++
8	15	M	Sept.	Penis	45 min.	99.8	21,400	Vomited 3 times, pain in knees and back; abdomen rigid ++++
9	52	M	Nov.	Penis	20 min.	99.6	7,400	Nausea, abdominal pain; slight abdominal rigidity
10	50	M	Nov.	Neck	30 min.	99.0	4,100	Pain in back, legs, abdomen; abdominal rigidity ++++
11	21	F	Nov.	Breast	30 min.	99.4	15,120	Vomited 2 times, cramping pains in abdomen and chest; pain in thighs and legs
12	22	M	May	Penis	½ hr.	100.0	12,250	Acute pain in abdomen, pain in thighs and back; ab- dominal rigidity ++++
13	19	M	June	Buttock	3 min.	101.0		Abdominal pain, no rigidity; increased tone
14	37	M	Aug.	Penis	30 min.	99.4	9,850	Cramps in legs, thighs, abdomen; abdominal rigidity +++
15	22	M	Sept.	Foot		98.8		

TABLE I—CONT'D

NO	AGE	SEX	MONTH	BODY LOCATION	TIME SYMPTOMS DEVELOPED	MAXIMUM TEMPERATURE (DEGREES F.)	W B C	SYMPTOMS
16	35	M		Buttock				Abdominal pain, rigidity
17	37	F	May	Buttock	½ hr		8,850	Abdominal cramps
18	22	M	May	Arm	½ hr	103.0	14,250	Abdominal pain and rigidity
19	29	M	Oct	Wrist	1 hr			Pain in arm and abdomen; abdominal rigidity ++
20	29	M	July	Penis	½ hr	100.0	11,300	Pain in abdomen and chest, and headache; abdominal rigidity ++
21*	37	M	Aug	Knee		98.8		Abdominal rigidity ++++
22	40	M	Sept			98.8		
23	50	M	June			100.0		
24	20	M	Aug.	Penis	½ hr.	97.0		Abdominal pain and rigidity
25	40	M	Oct.	Foot	5 hr.	100.0	20,000	Vomited once, pain in hips, abdomen, back; abdominal rigidity ++++; <i>no distension</i>
26	27	M	Oct	Penis	½ hr	102.4	5,300	Pain in hips and back, abdomen flat, abdominal rigidity ++++
27	45	M	Oct		½ hr.		8,200	Pain in legs, hips, abdomen; abdominal rigidity ++++
28	44	F	Oct	Leg	1 hr	101.8	7,900	Generalized aching, abdominal colic 4 hours after bite
29	22	M	Oct	Scrotum	10 min	100.0	12,700	Nausea, <i>no vomiting</i> , severe abdominal pain, abdomen distended, tender, some rigidity, aching in legs, back, and chest
30	40	M	May	Penis	½ hr.	99.0	8,200	Pain in inguinal region, through chest and abdomen, abdominal rigidity +++
31	19	M	July	Anilla		99.4		Cramps in abdomen and back, abdominal rigidity ++++
32	20	M	Nov	Toe	10 min	98.8		Neck pain
33	16	M	June	Back		100.0	15,050	Severe pain in groin, abdominal rigidity ++
34	31					100.0	11,550	Abdominal cramps and rigidity ++
35							12,800	Pain in back and abdomen, abdominal rigidity ++

35	12	M	April		10 min.	100.4	10,600	Pain in back and abdomen
36	50	M	May			98.8		Cramps in leg and abdomen
37	22	M	April	Scrotum			8,750	Abdominal pain and rigidity; tenderness
38	32	M	July				11,400	Generalized aching; abdominal cramps and rigidity
39	38	M	Aug.	Penis	10 min.	99.4	7,800	++
40	19	M	Oct.	Toe	10 min.	99.0	10,200	Pain in hips, abdomen, and epigastrium; not tender but rigid +++
41	19	M	April	Penis	10 min.	100.2		Abdominal rigidity +++
42	18	F	June			99.6	7,350	Pain in back and abdomen, no tenderness; abdominal rigidity
43	26	M	April		45 min.	99.4		Severe abdominal pain, no vomiting; abdominal rigidity
44	12	M	Oct.	Hip	30 min.	100.0	9,500	+++
45	12	M	Oct.	Arm	30 min.	101.0	6,900	Severe cramps in hip and abdomen; abdominal rigidity
46	10	F	Nov.	Thigh	1½ hr.	100.0	21,000	+++
47	46	M	Dec.	Ankle	3½ hr.	100.2		Severe pain in hips and abdomen; abdominal rigidity
48	28	M	Nov.	Penis	2 hr.	101.0	7,400	+++
49	31	F	Nov.	Nose		99.4		Pain in hips and abdomen; abdominal rigidity +++
50	48	M	Nov.	Nose	½ hr.	99.0		Chest pain
51	64	M	Oct.	Forehead	1 hr.	99.2		Pain in neck, abdomen, and chest
52	15	F	Oct.			98.8		Muscle cramps in extremities; abdominal cramps
53	2	M	June	Penis		101.0		Pain in head and neck
54	67	M	July	Penis	1 hr.	99.0	11,700	Infection of penis for four days; seen 4 days after bite
55	58	M	June	Scrotum	2 hr. mild 10 hr. severe	101.0	5,850	Severe upper abdominal pain with rigidity ++++; vomiting
56	28	M	Nov.	Arm		98.8		Back and abdominal pain; abdominal rigidity

•Exploratory laparotomy—preoperative diagnosis, perforated ulcer.

†Exploratory laparotomy—preoperative diagnosis, perforated appendix.

The therapeutic agents used varied considerably in the series. Morphine, atropine, magnesium sulfate, calcium gluconate, specific antiserum, and repeated hot baths were among the methods used. Morphine, hot baths, and specific antiserum when given relatively early seemed more advantageous in treatment than the other methods. Two patients were subjected to celiotomy, the preoperative diagnosis being perforated ulcer in one and perforated appendix in the other. There were no fatalities in this series.

#### SUMMARY AND CONCLUSIONS

The severity and predominance of abdominal symptoms and signs in patients with arachnidism make it necessary that surgeons have a clear conception of the condition if needless operations are to be avoided. Patients, although aware of spider bite, often fail to realize the causal relationship between bite and symptoms. The absence of abdominal tenderness and the presence of movement of the abdomen with respiration are important differential features in recognizing the syndrome. Specific antiserum given early after the bite seems to be the most rational therapy at this time. Fifty-six cases without a fatality are reported.

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# AN EVALUATION OF SOME OF THE MATERIALS COMMONLY USED FOR THE PREOPERATIVE PREPARATION OF THE SKIN\*

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THAT methods for evaluation of skin antiseptics have been generally unsatisfactory is evidenced by the voluminous literature on the subject and by the great variety of antiseptics which are employed for skin preparation in hospitals throughout the country. The main reason for this unsatisfactory state of affairs is that the conventional methods of evaluating skin antiseptics in vitro, while failing to meet the practical test of the action of the antiseptic on the skin, have nevertheless been used to promote the sale of commercial antiseptics.

At the same time, with so many far more dramatic fields of research open to the student of surgical problems, the investigation of skin antiseptics has not been systemically pursued by many individuals with adequate bacteriologic equipment and, at the same time, the point of view of the practicing surgeon. The work of Philip Price, of Baltimore, is the outstanding exception.

In choosing an agent for skin sterilization, the surgeon may relegate to positions of secondary importance the assembled data on the test-tube effectiveness of the various preparations, since the conditions employed resemble only in remote fashion the conditions provided by the skin itself. Furthermore, the surgeon will bear in mind the practical conditions under which antiseptics are employed clinically, particularly for supplementing the cleansing action of the preoperative scrub, and for preparing the skin of the operative field. The surgeon will require that the substance be active against skin flora, whether pathogenic or nonpathogenic, since the distinction is only a relative one; that it have a low surface tension, so as to make intimate contact with the skin; that it be active in the presence of organic material *and soap*; that it do more than produce a sterile film on the skin surface, beneath which bacterial proliferation continues; that it not be irritating to the scrubbed skin; and, finally, that the cost of the quantity necessary for practical conditions should not be excessive.

It might have appeared unlikely that any experimental method could be found which would simultaneously take into consideration all of the

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above factors. However, at about the time we decided that some work must be done on this problem, Price published a new method which seemed to us to provide new and sound principles, and we, therefore, used his technique as a starting point in our own work.

In the Price method, counts of the number of bacteria washed off during each of a series of one-minute scrubs are obtained by subjecting the wash water from each period to a standard plate count procedure. After determining the standard rate of removal of bacteria from the skin with soap and water alone, one may apply any given antiseptic and see to what extent this antiseptic modifies the subsequent rate of removal of bacteria. The advantage of this method is that it actually tests the antiseptic on the skin; and, by modifying the time of application of the antiseptic and by using many individuals as test subjects, it is possible to take into consideration all of the factors which were indicated above. The chief disadvantages of the technique are that it is very tedious and the production of results is necessarily slow because no one individual can carry out more than one experiment per week. The latter limitation is a result of the necessity for allowing time for regeneration of skin flora after vigorous scrubbing and "degermation."

#### METHOD

In order to simplify the description of the experimental technique which was finally adopted we will list the essential materials and supplies:

- 15 sterile basins
- 15 sterile brushes
- 15 lots of Ivory Snow, 1 Gm. each
- Tubes of broth culture media, 4 c.c. each\*
- Tubes of melted nutrient agar, 9 c.c. each†
- Sterile enamel cups for antiseptics under test
- Sterile gauze sponges and sterile towels

*Procedure.*—The "scrubber" stands on one side of a laboratory table placed adjacent to the sink, and facing the assistant. Necessary materials are arranged within reach. After preliminary moistening of the forearms and hands, 1 Gm. of Ivory Snow is placed on a moistened sterile brush and a cycle of scrubbing is commenced which is accurately timed with a stop watch. After a few seconds devoted to working up

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\*Neopeptone broth:  
 Distilled water 1 L.  
 Neopeptone 25 Gm.  
 Dextrose 0.5 Gm.  
 Adjust pH to 7.3

†Nutrient agar:  
 Distilled water 1 L.  
 Neopeptone 1 Gm.  
 Sodium chloride 8.5 Gm.  
 Glycerin 10 c.c.  
 Agar 15 Gm.

Adjust pH to 7.4 or 7.8  
 Add 0.5 c.c. horse serum to melted agar immediately before pouring plate

a lather in the moistened palm, the palm and fingers are scrubbed for five seconds; the nails for five seconds; the back of the hand for five seconds, and the forearm for fifteen seconds. The brush is then placed in the scrubbed hand and a similar procedure is carried out on the other hand and arm. The assistant then rinses the lather from the hands and forearms with a liter of tap water, the rinse water being collected in a sterile basin. The assistant withdraws two 1 c.c. samples of wash water and places them in each of two tubes of broth in order to remove the bacteria, as rapidly as possible, from the concentrated solution of soap. While the assistant is carrying out this procedure, the scrubber selects another brush and prepares to carry out another cycle of scrubbing. These cycles may be repeated for as many intervals as desired. In obtaining control data on soap and water alone, it is necessary to have about fifteen of these cycles. In experiments involving evaluation of an antiseptic, the scrubbing cycles are interrupted at some arbitrary interval, such as at the end of ten minutes or cycles. At this time, the hands and forearms are thoroughly dried with a sterile towel. The antiseptic is applied with a saturated sponge, the period of application being timed with a stop watch. In our experiments, we have also timed the period of drying of the antiseptic. Any unfixed antiseptic is then washed off with a liter of tap water and the series of scrubbing cycles is resumed, usually for five additional minutes. After completion of the entire period of scrubbing, the tubes of broth are thoroughly shaken exactly forty times with violent agitation and 1 c.c. of the mixture of soapy water and broth is placed in a tube of melted agar. The agar is poured out into a Petri dish which is subjected to standard manipulation in order to obtain uniform distribution of its contents. The agar plates are allowed to harden and are then incubated in an inverted position for forty-eight hours at  $37.5^{\circ}\text{C}$ . After the plates are counted, it is possible, after averaging the values of each pair of plates, to calculate the number of bacteria per cubic centimeter of wash water at each specific phase of the scrubbing period.

This procedure differs from Price's method in employing measured quantities of water and soap and in the use of individual sterile brushes for each scrubbing cycle. We have also provided for rapid separation of the test sample from the soapy water in order to avoid the deleterious effect of the alkaline soapy solution on the bacteria. These modifications do not alter the basic principle of the procedure, but are designed to improve the accuracy of the results.

*Method of Calculation.*—In Price's reports, the results of each scrub are subjected to a rather complicated mathematical procedure through which he arrives at an estimate of the total number of bacteria remaining on the skin of the hands and forearms at each given cycle in the scrubbing period. Even with the revision in methods of procedure which we have employed, we have not been able to satisfy ourselves that the experimental technique is of sufficient mathematical accuracy

to justify this type of computation. There is so much variation between individuals and between different scrubs by the same individual, that any final conclusion must be based on averages of many experiments if it is to enjoy real significance. After trying out a number of different methods of calculation, we finally concluded that the one most satisfactory, within the limits of accuracy of the procedure, is as follows.

1. We have ignored the wash water counts obtained during the first five minutes of scrubbing. This is the time during which the greatest variation takes place, and the magnitude of the counts is dependent upon many variable factors, most important of these being the length of the time interval since the preceding scrub.

*Colonies  
per cc.*

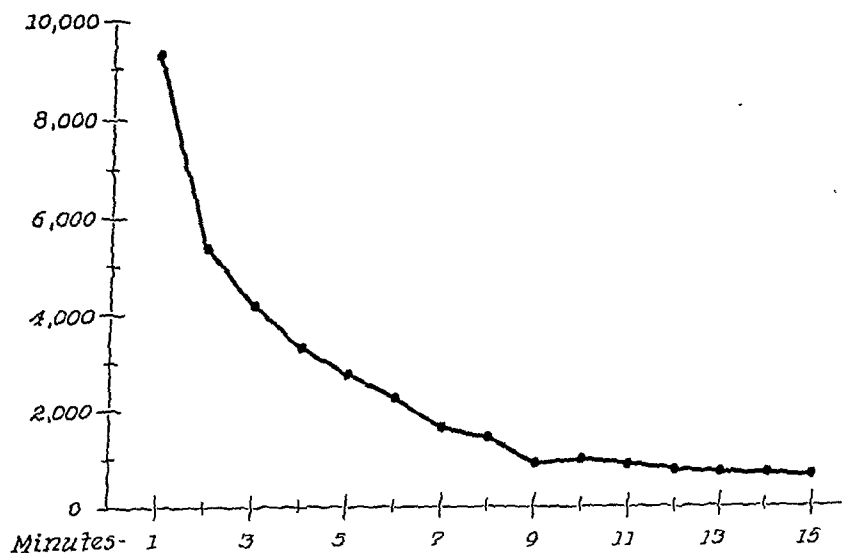


Fig. 1.—Determination of  $R_1$  for average of thirty-six scrubbing experiments of fifteen minutes each.

2. We have found in 226 experiments that the number of bacteria removed during the second five minutes of scrubbing is reasonably constant for different individuals and in different scrubs by the same individual. The average rate of removal of organisms is about 1200 per c.c. per minute or cycle during the eighth minute or cycle, and about 900 per c.c. during the tenth minute. At this point the disappearance curve tends to approach the horizontal (Fig. 1). Even though scrubbing with soap and water alone is continued for as long as thirty minutes, one would continue to remove bacteria at the rate of about 200 per c.c. per minute. We have designated the curve represented by the second five minutes of scrubbing as  $R_1$ , a curve which drops from the value of roughly 1800 per c.c. per minute during the sixth minute to about 900



per c.c. per minute during the tenth minute. An additional five minutes' scrubbing would reduce this to about 600 per c.c. per minute.  $R_2$  designates the final five minutes or cycles of scrubbing *after the application of the antiseptic*. Since the curve is almost horizontal at this point, particularly after the application of an effective antiseptic, one may average together the bacterial counts for the last five minutes into a single figure for each of the experiments. When values for  $R_2$  from a number of different experiments with the same antiseptic are averaged together, one arrives at a figure which characterizes the effectiveness of the antiseptic agent. The acceptability of this method of calculation is due to the fact that the best skin antiseptics afford  $R_2$  values of less than 10 bacteria per cubic centimeter per minute in contrast to the control values which are never less than 500 to 600 bacteria per cubic centimeter per minute. The lower the value of  $R_2$ , the greater the effect of the antiseptic. The validity of this conclusion depends in part upon the reasonable but unproved assumption that the rate of removal of pathogenic bacteria from the skin at any given time is dependent upon the number of living bacteria on the skin at that time.<sup>5</sup>

## RESULTS

In order to simplify the presentation of a somewhat unwieldy mass of data, we present Tables I, II, and III. These state the number of

TABLE I

DETERMINATIONS OF  $R_2$  FOR SOME COMMERCIALLY AVAILABLE ANTISEPTICS\*

SUBSTANCE	NO. OF EXPERIMENTS	AVERAGE $R_2$	RANGE OF $R_2$
Tincture "Q" p chloro symm m dimethyl hydroxy benzene p tert amyl hydroxy benzene and neutral soap. Solu tion 5% in 70% alcohol by weight	3†	168	90-240†
Tincture "Q" 1% aqueous solution	4	377	197-636
Tincture "Q" 5%	6	270	145-423†
Tincture "X" Mixture of high molecular alkyl dimethylbenzyl ammonium chlo rides	3†	220	123-265
Tincture "S" 2 Furfylmercuric hydroxide	6	123	68-200
Tincture "V" 1% 4 Nitro anhydro hydroxymercuri ortho cresol	4	137	37-270
Tincture "T" Secondary amyl trieresols .1% ortho hydroxyphenyl mercuric chloride .1%	3†	79	30-106
70% Ethyl alcohol by weight	9	194	85-415
95% Ethyl alcohol	4	86	17-169

\*1 minute exposures (30 second application, 30 second drying).

†Series not complete.

‡Marked irritation.

experiments of each type, the average value for  $R_2$  for these experiments, and the range of variation of the  $R_2$  figures. Table I concerns experiments in which the antiseptic was applied for thirty seconds and allowed to dry for thirty seconds. Table II is concerned with a larger number of experiments in which the antiseptics were applied for two minutes and allowed to dry for two minutes. It is noted that in some cases the range of variation is great, whereas, in others, all of the values obtained in seven to nine experiments are consistently low.

TABLE II  
DETERMINATIONS OF  $R_2$  FOR SOME COMMERCIALY AVAILABLE ANTISEPTICS\*

SUBSTANCE	NO. OF EXPERIMENTS	AVERAGE $R_2$	RANGE $R_2$
Tincture "X"	6	111	17-242
Tincture "U"	9	123	20-463
Sodium ethyl-mercuri-thiosalicylate			
Tincture "V"	9	32	5- 55
Tincture "W"	7	35	24- 68‡
Tincture "T"	9	27	6- 66
Tincture "S"	9	24	7- 47
Chrysoidin Y mixture	9	46	19- 80‡
70% Isopropyl alcohol	9	20	21- 31
70% Ethyl alcohol (by weight)	10	18	3- 56
95% Ethyl alcohol	10	12	6- 27
Tincture iodine followed by 95% ethyl alcohol†	7	7	5- 9

\*1 minute exposures (2 minute applications; 2 minute drying).

†Iodine applied for 30 seconds.

‡Marked irritation.

*Time of Application.*—A glance at Tables I and II shows that the  $R_2$  values are much lower with four minutes' exposure than with one minute exposure. Furthermore, it seems to be generally true that the agents which are most effective with the brief period of exposure are also most effective with the longer period of exposure. Besides emphasizing the obvious importance of the time of action in chemical antiseptics, this relationship of the figures tends to uphold the general validity of the technique.

*Mercurial Agents.*—Five proprietary tinctures of mercurial antiseptics were included among the agents studied. It was pointed out by Price<sup>4</sup> that some mercurial agents, particularly bichloride of mercury, are capable of producing a sterile surface on the skin as a result of the formation of a surface coagulum which may remain intact for a considerable period of time. However, it was believed that bacterial proliferation could take place at an active rate beneath this film, and that the end result would likely be a higher population of bacteria in the skin than would have been the case had the mercurial agent not been applied. One advantage of the experimental technique employed by Price and by us is that vigorous mechanical scrubbing will remove this surface film and release bacteria which might otherwise remain behind the superficial barrier. No data were obtained concerning the duration

of the action of the several agents, our emphasis being placed primarily on the immediate effect.

The mercurial antiseptics employed as the commercial tinctures were, as a group, in the intermediate range of effectiveness, as shown in Table II. Of these agents, tincture S showed a slight, though possibly significant, advantage over the other agents in this group, namely tinctures T, U, V, and W. Tincture U appeared quite consistently to be the least effective of the mercurial preparations. Where the period of exposure to the antiseptic was only one minute, the differences between the several mercury-containing preparations are not significant, although tincture T appeared to be most active. The vehicle of tincture S was tested and was found to have an average  $R_2$  in four experiments of 113 with a range of 74 to 138, indicating that it was markedly less effective than the complete preparation.

*Chrysoidin Y Mixture*.<sup>\*</sup>—Slightly less effective than the mercurial agents was chrysoidin Y mixture, which happens to be an antiseptic now in common use in several Philadelphia hospitals. The average  $R_2$  figure of forty-six is higher than four out of five of the mercurial agents. Though one of the prevailing arguments for its clinical use, in addition to its recognized inexpensiveness, has been its freedom from irritation, it was noted that the application of this substance to the skin for four minutes resulted in irritation, particularly of the skin of those individuals with light complexions.

*Tincture X*.—The agent, tincture X, has been the subject of a number of highly enthusiastic reports<sup>3, 6</sup> and there is no question but that under certain experimental conditions it possesses very powerful antiseptic qualities. However, in our hands, it has been a decidedly limited value when applied to the freshly scrubbed skin. This is possibly due to the fact that it is known to be inactivated by soap.<sup>3</sup> We made no attempt to exclude soap from the skin before applying any of the antiseptics because of the fact that soap is still the detergent most commonly used in preoperative skin preparation. It would seem most undesirable to rely for skin sterilization on an agent which was incompatible with traces of soap. This does not imply that tincture X may not be of definite value in other types of sterilization.

*Alcohols*.—As a group, the most effective preparations were the alcohols. This fact coincides with the findings of Price.<sup>2</sup> He recommended the use of ethyl alcohol of 70 per cent by weight, and believed that the effectiveness of the alcohol might possibly be increased by adding a certain amount of isopropyl alcohol.<sup>2</sup> In our experiments, the effectiveness of 70 per cent alcohol by weight was exceeded only by that of 95 per cent ethyl alcohol. In this respect, our findings differ from those of

*Chrysoidin Y	2	Gm.
Bichloride of mercury	1	Gm.
Concentrated HCl	7.5	c.c.
Acetone	100.0	c.c.
Ethyl alcohol	525.0	c.c.
Distilled water, q.s.	1,000	c.c.

Price, and from the prevailing impression that 70 per cent alcohol is a more effective antiseptic than is 95 per cent alcohol. When exposure was limited to one minute, 95 per cent alcohol appeared to be very much more effective than 70 per cent alcohol. The difference was not as significant when the period of exposure was increased to four minutes. It was observed that when the 95 per cent alcohol was allowed to dry, the  $R_2$  tended to be lower than was the case when water was applied before the drying of the alcohol had been completed. When the drying was not completed, there appeared little difference between 70 per cent by weight alcohol and 95 per cent alcohol (Table III). Seventy per cent isopropyl alcohol possessed approximately the same degree of antiseptic effectiveness as 70 per cent by weight ethyl alcohol.

TABLE III  
DETERMINATIONS OF  $R_2$  FOR ETHYL ALCOHOL\*

SUBSTANCE	NO. OF EXPERIMENTS	AVERAGE $R_2$	RANGE $R_2$
95% Ethyl alcohol			
Allowed to dry	10	12	6-27
Drying avoided	4	26	17-48
70% Ethyl alcohol (by weight)			
Allowed to dry	10	18	3-56
Drying avoided	3†	21	18-24

\*Two minute exposures.

†Series not complete.

*Iodine.*—The effectiveness of 95 per cent alcohol was increased slightly but definitely by a preliminary application of tincture of iodine. In seven experiments with iodine followed by 95 per cent alcohol, the average  $R_2$  was seven and the maximum  $R_2$  obtained was nine. Both in respect to the average figure and the maximum figure, this combination of iodine and 95 per cent alcohol was superior to any other preparation studied. Iodine is the antiseptic which has probably enjoyed more general use over a long period of time than any of the other skin antiseptics. It is interesting to note that laboratory studies of the type here reported serve to point out that the trend away from iodine to more expensive and complicated preparations has not been based on sound evidence. While iodine is undesirable for use by the surgeon in preparation of the skin of the hands and forearms because of its staining properties, there is every reason to believe that tincture of iodine is the most desirable agent for preparation of the skin of patients in the operating room. According to our figures, it may be desirable to remove the tincture of iodine with 95 per cent alcohol in order both to reduce the irritating properties of the iodine and also to augment the effectiveness of the skin preparation.

*Tincture Q.*\*—A modified phenol preparation known to be compatible with soap was included in the series in order to have data on a repre-

\*Kindly supplied by Lehn & Fink Products Corp., Bloomfield, N. J., under the trade name, "Amphyl," through the courtesy of Dr. E. G. Klarmann.

sentative of this group. The material studied was a preparation containing p-chloro-symm.m-dimethyl-hydroxy-benzene, p-tert. amyl-hydroxy benzene and neutral soap. Both aqueous solutions and tinctures of this preparation were studied. It proved to be virtually without effect on the skin, and, in fact, the vehicle in which the tincture was dissolved proved to be just as effective as the tincture containing the supposedly active agent. When the strength of the material was increased to a point at which some slight degree of effectiveness appeared, the preparations were found to be quite irritating to the skin and could not be tolerated. When a 5 per cent tincture of the material was incorporated with 70 per cent by weight ethyl alcohol, conceded to be an effective antiseptic, the resulting mixture was found to be almost identical in effectiveness with the 70 per cent alcohol alone.

#### DISCUSSION

Although it would be desirable to have a method of evaluating skin antiseptics by which comparison might be made on a more accurate mathematical basis than that here described, we are inclined to believe that this comes as close to providing a simple and satisfactory test method as any that has been put forward. In its future application, the method could undoubtedly be simplified. For example, if a preliminary scrub of ten minutes were carefully conducted, the antiseptic then applied, and careful bacterial counts obtained on the wash water for a period of five minutes after the application of the antiseptic, a series of reduplicated tests would provide a satisfactory estimation of the practical efficiency of any agent proposed for skin sterilization. We emphasize the necessity for carrying out bacterial counts for at least five successive minutes of scrubbing in order to eliminate sources of error inherent in any method of collecting and counting bacteria. Furthermore, it is desirable that the tests be carried out by several different individuals and that a total of at least four experiments be carried out with each individual preparation if reliable interpretations are to be obtained. It must be emphasized that satisfactory results will only be obtained if the scrubbing cycles are conducted with careful precision, and if the bacteriologic procedure is carried out in accordance with sound practices.

It is not the purpose of this paper to enter into a discussion of the reasons why the alcohol preparations appear to be more effective than any of the commercial antiseptics tested. While skin preparation is unquestionably the widest field of use for chemical antiseptics of the types here considered, there are undoubtedly certain fields of usefulness for antiseptics in which alcohol is entirely unsuitable. Furthermore, it is possible to use alcohol in strengths of 70 to 95 per cent, while the concentration of active agent in most tinctures is only a fraction of 1 per cent. The surgeon is concerned, however, with the elementary question of what method of preparation will result in the least possible number of living organisms on the skin of the operating personnel and on the

skin at the site of the operation. Furthermore, he must rely on agents which will be well tolerated by the skin and, in testing them, must employ the concentrations sold commercially. With these considerations in mind, we are inclined to recommend that principal reliance be placed on soap and water and ethyl alcohol in the preparation of the skin of operating personnel. Since the skin of the patient is not scrubbed for ten minutes, it is probably advantageous to precede the alcohol treatment with an application of 3.5 per cent tincture of iodine. The ideal concentration of alcohol is 95 per cent, but, for reasons of economy, it may be necessary to reduce the concentration to 70 per cent by weight. Such a compromise can be made without sacrificing more than a fraction of the effectiveness of the material.

We urge, also, that in the use of alcohol and in other skin antiseptics, the surgeon recognize the fundamental importance of the factor of time. Two minutes of continuous application of the alcohol to the skin is desirable, preferably accompanied by mechanical rubbing. The alcohol should be left to evaporate in order further to extend the period of its actions.

#### CONCLUSION

Through a modification of the Price technique by which the effectiveness of antiseptics on freshly scrubbed skin is evaluated, it is concluded that ethyl alcohol in strengths of 95 per cent and 70 per cent by weight is preferable to any of a group of commercially prepared agents specifically designed for skin sterilization.

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## RESECTION OF THE COLON IN SIX CASES OF HIRSCHSPRUNG'S DISEASE

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THE treatment of Hirschsprung's disease has undergone some changes in the last two decades. While it is certain that no one form of treatment is helpful to all cases, there is now, with more variety of treatment, a greater chance of benefiting every patient. However, medical management was very unsatisfactory until the development of the newer autonomic system drugs such as the parasympathetic drug, mechohyl (Law<sup>1</sup>), and sympathetic drug, syntropan (Klingman<sup>2</sup>). Since Law's<sup>1</sup> report, in 1940, not many cases in which this treatment was used have appeared in the literature but it is likely more will. Drug therapy is in large part a trial-and-error type of treatment as there is no way of being certain whether the parasympathetic system is underactive or the sympathetic overactive, although spinal anesthesia may be diagnostic in determining overactivity of the sympathetic system. However, one drug or the other is usually helpful in the mild or early cases and possibly could keep the condition in check if begun early in infancy.

Since 1927, when Wade and Royle<sup>3</sup> reported the first operation for removal of the lumbar sympathetic ganglion in the megacolon, surgical treatment of Hirschsprung's disease has consisted primarily of this operation. The literature since 1930 has contained an increasing number of reported "cures" of megacolon and even chronic constipation following this operation. One wonders how many failures are omitted from the literature. The operation for resection of the affected part of the colon is mentioned only to be condemned except in the report by Dixon<sup>4</sup> and in the book by Ladd and Gross.<sup>5</sup>

The two main reasons for the disrepute of this operation are first, the high operative mortality and second, the likelihood that the condition may recur in the portion of the colon remaining. Perhaps the first situation may have been true fifteen or twenty years ago but should not be now. We are of the opinion that the second can perhaps be prevented by the better medical program now available.

Of pediatric as well as surgical interest is the variability of signs of Hirschsprung's disease in the first few weeks of life. At times the onset

of constipation and distention may be late and the presenting sign may be vomiting. In our series of six cases the early severe vomiting was a pronounced feature in four (Cases 1, 2, 3, and 4) of the infants. This may be just another manifestation of motor imbalance of the gastrointestinal tract which as it progresses tends to localize in the lower rather than the upper tract.

Since two of our patients did not respond to bilateral lumbar sympathectomy and the other four did not respond satisfactorily to medical treatment, surgical resections were done. In the following case reports all laboratory reports were normal except as indicated. Proctoscopic examination was routine and was always negative for any evidence of obstruction. The sigmoid was uniformly dilated. The pathologic report on the resected portions of colon was similar in all cases, that is, muscular hypertrophy with round cell infiltration and no change in nerve cells. These findings were typical of those of Hirschsprung's disease.

#### CASE REPORTS

CASE 1.—T. P., a male, first entered this hospital Sept. 22, 1924, at 6 days of age, with the chief complaint of vomiting and refusal to nurse for three days. The abdomen was moderately distended and there were slow peristaltic waves from the left costal margin to the umbilicus. Projectile vomiting occurred two or three times daily while in the hospital.

The second entry was at the age of 3 months. The chief complaint then was constipation. Barium enema was done, this time revealing the colon to be of large caliber with an elongated dilated sigmoid loop.

In a follow-up note at the age of 4 years he was reported to be having but one bowel movement per week and that following enema. Six months later he had a complete obstruction due to fecal impaction.

The next admission was at 7½ years of age. At that time the complaints consisted of vomiting, no bowel movements without enemas, anorexia, and loss of weight. Repeated barium enema showed the colon to be dilated to three times normal size from the mid-transverse colon to the lower half of the sigmoid. Spinal anesthesia was given with 60 mg. of neocaine without any change in the colon. Bilateral lumbar sympathectomy was done on March 12, 1932, through the abdominal approach. At operation it was noted that the sigmoid and lower two-thirds of the descending colon were very large and distended with pale, grayish thickened walls. Spontaneous bowel movements occurred within the few weeks after operation. For the next four years he continued to have daily bowel movements with the use of mineral oil and cascara nightly. Fecal impaction then occurred requiring hospitalization.

Two weeks later, at the age of 12, he was again hospitalized because of volvulus of the sigmoid colon and fecal impaction. At this time a three-stage Mikulicz procedure with resection of the sigmoid colon was done. Recovery from this operation was uneventful and he was again having normal bowel movements on discharge.

One year later he was again hospitalized for fecal impaction. Barium enema at this time showed a narrowed area at the junction of the descending colon and rectum. Proximal to this point the colon was atonic and dilated excessively. The descending, transverse, and ascending colon and cecum were normal in length but abnormally wide. There was surprisingly good emptying of the bowel following defecation.

Thereafter, he was seen in the outpatient department, usually for some complaint not referable to the primary disturbance. When last seen, at the age of 17



years, he was reported to be in good health with good appetite, normal weight, and an abdomen that was flat and soft. Occasionally he had mild episodes of constipation relieved by laxatives. Thus, for five years he has had a fairly normal course regarding bowel habits.

This case was unsuccessful after a sympathectomy; it presented one of the dangers, that is, obstruction due to volvulus. It was interesting to note the change in disposition when the patient's bowels were functioning normally as contrasted to a sullen, toxic-looking chap when he had a fecal impaction.

Fig. 1 shows the x-ray study of his large bowel in 1940. While there is dilatation of the bowel, as shown, he has normal bowel habit.



Fig. 1 (Case 1).—X-ray taken Feb. 2, 1940.

CASE 2.—G. V., a female, was admitted to this hospital for the first time at the age of 3 weeks. She was vomiting frequently and had lost weight. Bowel movements were infrequent and obtained only after suppositories. Barium enema showed a spastic narrowed rectum with slightly dilated atonic colon and abnormally dilated ileum. She was admitted twice more in the next three months because of increase of vomiting and constipation. At the age of 2 months a spinal anesthesia and barium enema were done with no increase in expulsion of stool.

At the age of 6 months the vomiting again became severe and there was no stool even with milk of magnesia and mineral oil. At this time the abdominal distention was first observed and there were visible peristaltic waves. Barium enema and spinal anesthesia were repeated without beneficial results. After this admission the infant was brought to the outpatient department for colonic flushes as the home care was inadequate. Outpatient department visits became infrequent and when next seen at the age of  $4\frac{1}{2}$  years it was reported that she had done fairly well in the

interim with mineral oil, laxatives, and enemas. At that time barium enema showed marked dilatation of the whole bowel. Surgery was advised.

Her fifth admission was on March 1, 1939, at the age of 5 years. Following preliminary cleansing of the colon a Mikulicz procedure was done with resection of 72.5 cm. of large bowel from the sigmoid up to the mid-transverse colon. The postoperative course was uneventful. On discharge she was having spontaneous daily bowel movement. Six weeks later she returned with a fecal impaction which was removed with oil retention enema.

A barium enema at the age of 6½ years showed considerable dilatation of the distal half of the transverse colon. In the next three months she had two episodes of fecal impaction, one so severe as to cause partial obstruction.

Nearly a year elapsed before her next hospital visit which was on Sept. 7, 1942. Her mother stated that she had been very well until three weeks before entry. Bowels had moved once or twice a day without mineral oil or laxatives. Flatulence had been quite marked. In the last few weeks her appetite had been impaired and there had been no bowel movement for three days. Laxatives had been given but caused abdominal pain and vomiting. On examination there was a large firm mass which took eleven days of mineral oil by mouth and rectum and a variety of different enemas to remove. Barium enema after apparent cleansing showed an orange-sized mass in the sigmoid and some difficulty of passage of the barium through the site of previous anastomosis in addition to a dilated colon. One week after discharge another fecal impaction occurred and this had to be broken up under anesthesia and removed manually. Surgery was again advised.

Cecostomy and appendectomy were done Oct. 3, 1942, and ten days later a complete colectomy was done. At operation the large bowel from the point of previous anastomosis to the cecum and the distal three inches of the ileum was dilated and thick walled. The terminal ileum was transected and an end-to-side anastomosis with the lower sigmoid done. There was a moderately stormy postoperative course with liquid stools, moderate distention, anorexia and weight loss, occasional emesis, and colicky abdominal pain. Much of this was relieved by prostigmine but recovery was slow with much distress.

She was home three weeks when there was a recurrence of colicky abdominal pain associated with vomiting. The abdomen was very distended with tremendous peristaltic waves. It was felt that she had partial obstruction probably at the site of previous anastomosis. The condition cleared in two days in the hospital.

This patient had very poor home care. She did very well as long as she was in the hospital and away from her parents.

CASE 3.—F. M., a male, was first admitted to this hospital on Sept. 11, 1940, at the age of 3 years, with the chief complaint of severe constipation and abdominal distention since infancy (see Fig. 2). His early history was interesting in that he was normal at birth and did very well for the first ten days. Vomiting then started and, four days later, severe diarrhea with profuse foul stools. In spite of various forms of treatment and many formula changes the diarrhea lasted for two weeks. During this time he lost weight so that at 1 month of age his weight was 4 pounds, or one-half of his birth weight. A soybean formula was tried and on this the diarrhea ceased and he began to gain weight. Within the next few weeks he became constipated and this progressed so that bowel movements were secured only with the use of laxatives. These were effective in producing three or four bowel movements per week for nearly two years but after that they were no longer effective and the mother resorted to enema. Meanwhile, there was progressive and marked enlargement of the abdomen.

At the time of entry the examination was not remarkable except for the huge abdomen which was doughy to palpation. On barium enema the colon was distended

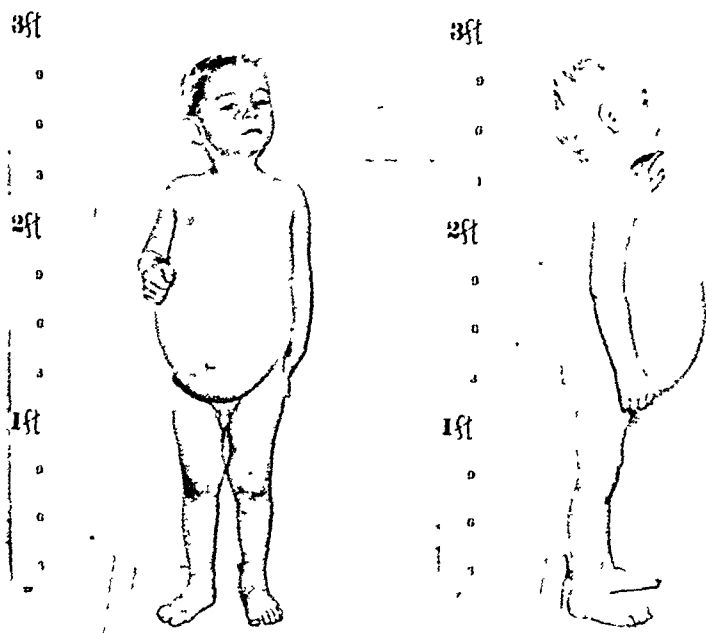


Fig. 2 (Case 3) —Taken Sept. 12, 1940, on first admission.

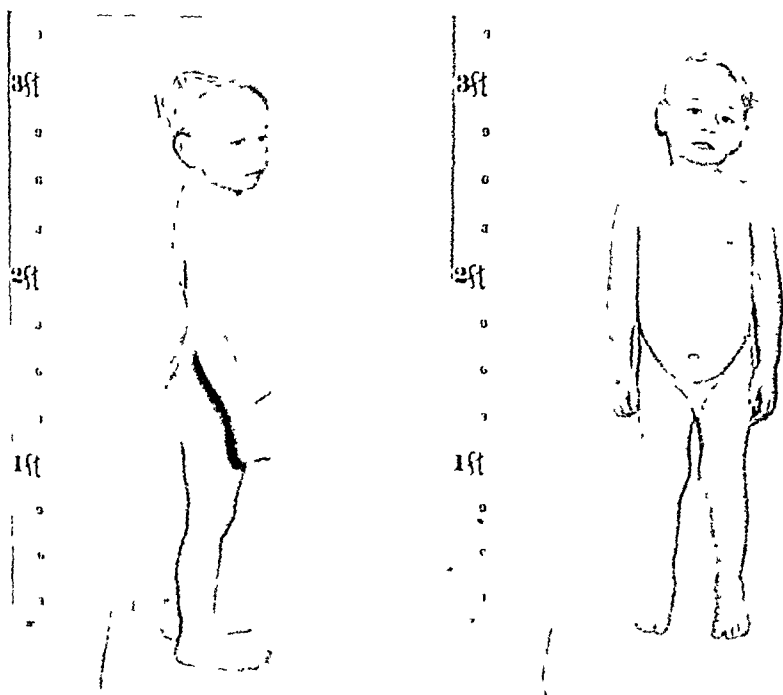


Fig. 3 (Case 3) —Taken July 10, 1941, nine months after sympathectomy.

throughout its entirety with the descending portion dilated up to 10 cm. in diameter. After four hours 90 per cent of the barium still remained in the colon.

He was given a six weeks' trial of medical treatment which consisted of non-residue diet, enema, vitamin B, physiotherapy to the abdominal muscles, mechloly up to 0.2 Gm. twice a day, plus prostigmine bromide 0.015 Gm. daily, and finally syn-



Fig. 5.

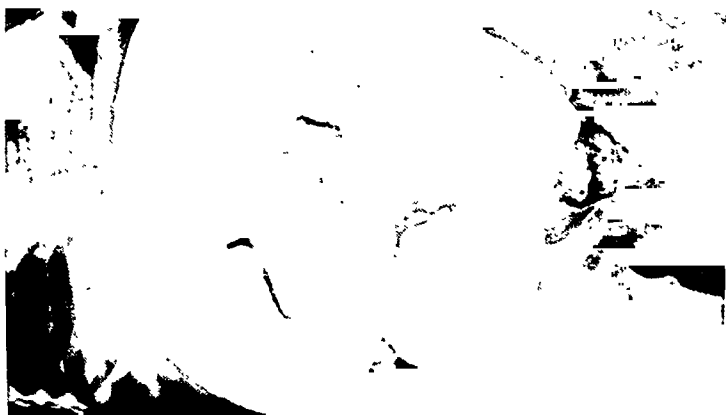


Fig. 4.

Fig. 4 (Case 3).—Barium enema nine months after sympathetomy.

Fig. 5 (Case 3).—Barium enema done Nov. 4, 1941, thirteen months after sympathetomy and after one year of medical treatment.

tropan 0.5 Gm. twice a day, but no spontaneous bowel movement occurred although a severe reaction to the drugs necessitated emergency use of atropine. Bilateral sympathetomy was decided upon and carried out on Nov. 5, 1940. At operation through the abdominal approach a tremendous sigmoid and left colon were seen. There was a change in the bowel wall at about the junction of the middle of the transverse colon

and at the middle sigmoid area. The bowel between was soggy, thick walled, and rather lifeless. The right colon appeared normal, though somewhat dilated. He made an uneventful recovery, though without spontaneous bowel movement.

Eight months later he was readmitted. He had gained weight and felt well but bowel movements were not normal, although occasionally he had a small one. A barium enema was repeated giving mecholyl and prostigmine but there was no increase in visible peristalsis. However, he was discharged on mecholyl 0.1 Gm. twice daily.

He was again hospitalized two months later, Sept. 29, 1941. The interval history was that he had been having bowel movements almost daily with the mecholyl though suppositories were frequently necessary to initiate them. When the supply of mecholyl was exhausted three weeks before re-entry, constipation recurred. In spite of resumption of mecholyl in doses up to 0.3 Gm. twice daily, there were no spontaneous bowel movements.



Fig. 6 (Case 3).—Resected specimen.

Since the family lived at a great distance from the hospital and were often isolated during the winter for days at a time, it was felt that with the risk of volvulus not remote, a colon resection should be undertaken. Therefore, a preliminary recostomy and appendectomy was done Nov. 10, 1941.

On Dec. 3, 1941, at the age of 4 years and 3 months, a left colon resection was done with an end-to-end anastomosis; 63 cm. of the colon were removed (see Fig. 6). Recovery was uneventful and was followed by daily spontaneous bowel movements. Fourteen months later, he was reported as having normal daily bowel movements.

CASE 4.—D. S., a male, was first admitted to this hospital on March 13, 1942, at the age of 3 years and 3 months. His chief complaints were abdominal distention since birth and constipation since the age of 6 months. Birth was normal but on the second day he began vomiting. This was projectile and stained yellow green. As this continued, a diagnosis of pyloric stenosis was made and an operation performed elsewhere on the eleventh day. Following the operation there was no further vomiting and stools were reported normal. However, on the fifth day abdominal distention became so marked that the sutures broke and the incision had to be repaired. The distention continued and considerable gas was passed by rectum but the infant seemed well otherwise.

At about 6 months of age constipation was first noted and this progressed as did the distention. Occasionally periods of diarrhea would occur. Early, mineral oil and laxatives were effective in control of constipation, but by 1 year of age only enemas produced passage of stool.

Examination was normal except for the abdominal findings of moderate distention especially of the left lower quadrant where peristaltic waves were visible and hard fecal masses palpable. Barium enema showed mild dilatation of the sigmoid. This was repeated under spinal anesthesia, showing that the colon emptied into the sigmoid which in turn was unable to discharge its contents into the rectum and so became more dilated.

He was treated with flushes and then mecholyl 0.1 Gm. twice daily. Later prostigmine bromide 0.015 was added. He developed a reaction to mecholyl after nine days, but no spontaneous bowel movement. He was also given vitamin B and colonic flushes.

Since the diseased portion of the bowel seemed so well localized, resection was advised. On April 14, 1942, an appendectomy and cecostomy were done and on May 1, 1942, a resection of the sigmoid loop (15 cm. in length) and end to end anastomosis. At surgery the sigmoid was found to be three or four times normal size with a thickened wall. The sigmoid with a margin of normal colon on either side was resected. Two grams of sulfanilamide were left in the abdominal cavity. Recovery was uneventful with normal bowel movements before discharge.

He was seen at intervals in the outpatient department during the next six months. He was having daily normal bowel movements and if occasionally one day missed, mineral oil corrected this. The only complaint was occasional soiling but this seemed a behavior situation rather than true incontinence.

CASE 5.—F. N., a female, was first admitted to this hospital on May 20, 1942, at the age of 4 years, with the chief complaint of constipation since the age of 5 months. Mineral oil and molasses given daily relieved the constipation for the succeeding five months. From the age of 10 months to 4 years enemas were necessary to produce a bowel movement. A low residue diet and vitamin B gave no relief. Mecholyl has been given in the few weeks preceding admission without results.

On admission the patient was very well developed and nourished. The only abnormal finding was the large protuberant abdomen which was doughy to palpation with large fecal masses palpable on the left side. Barium enema showed moderate dilatation of the sigmoid region. Colonic flushes were given to cleanse the colon and then the patient was given mecholyl 0.05 Gm. three times a day for ten days. Since the lesion was apparently well localized and failed to respond to medical treatment, surgery was decided upon. An appendectomy and cecostomy were done on June 3, 1942, and 13 cm. of sigmoid were resected on June 23, 1942. The large bowel appeared to be normal except in the region of the sigmoid where it was easy to demonstrate the difference between the thick walled soggy sigmoid and the normal bowel, both distal and proximal.

The postoperative course was uneventful and a normal bowel movement occurred

on the fourth postoperative day. Cecostomy was closed on the seventeenth postoperative day.

A follow-up on Feb. 1, 1943, showed a gain of five pounds, good appetite, and two to three formed stools daily without any medication.

CASE 6.—J. W., a male, was admitted to this hospital on July 17, 1942, for the first time, at the age of 6½ years. His early history was noteworthy in that he began having projectile vomiting the first few days after birth and this continued until the third month. Abnormal stools, infrequent but copious, were noted during the nursery period. Distention did not appear until the sixth week. Bowel movements occurred once to twice a week during the first two years in spite of the use of laxatives, vitamin B, and mineral oil. Colonic flushes were given every other day from the age of 2 years on.

On examination the patient was normal except for the tremendously enlarged abdomen with thin walls and easily palpable colon.

Treatment consisted of the routine cleansing procedure plus low residue diet and vitamin B. He was started on mecholyl and reached a dosage of 0.2 Gm. twice a day and then prostigmine bromide 0.015 Gm. was added with each dose of mecholyl. On this regime he had one single very small spontaneous bowel movement and no more. Barium enema under spinal anesthesia showed no change in the tremendously dilated colon.

Cecostomy as a preliminary to resection was done on August 15, 1942, and 90 cm. of the left colon were resected on September 2, with an end-to-end anastomosis. The diameter of the resected colon was 13.7 cm. There were enlarged nodes in the mesentery of both large and small bowel. The line of demarcation between diseased and normal bowel was quite distinct distally but less so proximally. Two grams of sulfanilamide were left in the peritoneal cavity and 1 Gm. in the wound. His postoperative course was somewhat stormy with vomiting, abdominal distention, and low-grade fever. However, the cecostomy was finally closed three weeks later and about that time he began to have almost daily bowel movements. He was discharged on Oct. 10, 1942.

He was readmitted two days later because of vomiting, abdominal pain, and temperature of 39° C. On examination he was dehydrated and obviously very ill. Abnormal findings on examination were a moderately injected pharynx and distended abdomen, which was tympanitic. There was slight para-umbilical tenderness but no rigidity. Rectal examination was not abnormal. The white blood count was 13,700 with 74 per cent polymorphonuclears. Plain film of the abdomen showed huge dilatation of the colon which was filled with gas and showed fluid levels. Thin barium showed no obstruction.

The patient was treated with intravenous fluids and Wangenstein suction. As there was no real improvement after two days of this therapy, an exploratory laparotomy was done. No mechanical obstruction was found. There was a very large group of nodes in the mesentery of the small bowel. The appendix was found to be very large and firm but not markedly inflamed; it was removed without difficulty. The site of the previous anastomosis was patent. The pathologic report was acute appendicitis with acute mesenteric adenitis.

Again the postoperative course was somewhat stormy with episodes of vomiting and distention. Transfusions and intravenous fluids were given as supportive treatment. Mecholyl and prostigmine were started on the ninth day. The following day he was given a large dose of prostigmine by error and shortly after this there was an emesis of 700 to 800 c.c. and a large stool of over 800 c.c. both formed and liquid. Subsequently his appetite returned, he gained weight, and had spontaneous daily stools. Report from his mother in February, 1943, stated that he was gaining weight, had a good appetite, and was having normal daily bowel movements.

## DISCUSSION

It is our plan now, in these early cases, to attempt to control the bowel habit by diet, vitamin B, mecholyl, or syntropan and colonic flushes if necessary; and if this is not adequate, to give a spinal anesthetic in the fluoroscopic room so as to watch the response of the colon. If there is no response from the anesthetic and the medical regime is inadequate, then the involved segments should be resected in two stages.

While mecholyl is a useful drug it is toxic and the dosage must be watched very carefully. We feel it might be well to have these patients continue on small doses in order to increase the bowel tone after discharge from the hospital.

## SUMMARY

This is a report of six cases of Hirschsprung's disease in patients between the ages of  $3\frac{1}{2}$  and 12 years, who had resection of the involved segments, without a death. This is partially luck but the close cooperation between the two departments is most important.

The results have been satisfactory in five. The patient in Case 2, who required a total colectomy, has not done so well.

In our hands sympathectomy or medical treatment alone or together has not been satisfactory.

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## POSTCHOLECYSTECTOMY RUPTURE OF THE COMMON BILE DUCT

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A REVIEW of the literature indicates that rupture of the common bile duct following cholecystectomy has been rarely described. In 1935, Newburger collected nine such cases proved at operation or necropsy and reported one of his own. All patients were women, their ages varying from 25 to 59 years. All had undergone cholecystectomy and choledochostomy except one, who had had only cholecystectomy. The point of rupture was the tied cystic duct stump in five instances, the point of drainage of the common duct in three instances, and elsewhere in the common duct in two instances. Stones were present in the common duct in seven cases, and were absent in the remaining three instances. The time of rupture following cholecystectomy varied widely, the shortest period being twelve days, the longest three and one-half years. In one case (Wolfson and Levine), a cholecystectomy had been performed twenty-five years previous to choledochostomy. Fifty-five days after the latter operation there was rupture of the common duct and bile peritonitis. This patient recovered following T-tube drainage of the common duct and had common duct stones removed a few months later. In all of the other patients referred to above death followed drainage of the extra-hepatic biliary tract instituted for the rupture.

Perforation, not the result of pressure from stone, of a diverticulum of the choledochus just below the cystic duct was described by Wernsdörfer in a man aged 40 years. Small stones were evacuated and the choledochus drained with a T tube; recovery ensued.

Recently Newell reported the instance of bile accumulation in the abdomen where at laparotomy no gross perforation of the extrahepatic biliary ducts or of the gall bladder was demonstrable, although the wall of the choledochus was edematous and infiltrated with bile-stained fluid, suggesting an extravasation from a minute or even healed perforation. This author cites Bailey's patient in whom the perforation was discovered only at necropsy and found to be on the posterior aspect of the junction of cystic and common ducts. Vale's case is also cited, in which there was extravasation of bile in the peritoneal cavity without gross evidence of perforation. Recovery followed drainage.

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In Reich's patient, a man aged 73 years, laparotomy revealed an extensive accumulation of bile-stained fluid in the peritoneal cavity and there was a perforation in the common hepatic duct. No concretions were present. Death ensued a few hours after laparotomy and necropsy revealed cirrhosis of the liver. The large extrahepatic bile ducts were not markedly diseased and the gall bladder was small and contracted.

Two additional instances of perforation of the common bile duct are cited below.

CASE 1.—M. C. (No. 284550), a woman aged 67 years, was admitted to Billings Hospital May 7, 1942, complaining of severe attacks of cholecystitis in January, 1941, with marked jaundice. In another institution, a cholecystostomy was performed in February, 1941, with evacuation of many concretions from the gall bladder and common duct. Following recurrence of another severe attack, a cholecystectomy was performed in April, 1941, and according to the history obtained a concretion was also removed from a diverticulum (?) of the common duct above the head of the pancreas. Since the second operation, the patient's condition was good until three days prior to the present admission, when a severe epigastric pain developed that radiated to the interscapular region. The next day icterus was apparent and the severe pain with nausea and vomiting persisted. The patient was brought to the hospital in an ambulance and appeared acutely ill. Temperature was 101° F. (rectal); W.B.C., 18,650; Icteric index, 19.5; N.P.N., 111 mg. per cent; pulse, 72; B.P., 100/70. General abdominal tenderness was noted with no rigidity or palpable masses; some distension was present. Parenteral glucose and saline solutions were administered and the next day the patient felt slightly improved. During the next four days the temperature rose gradually to 103° F. (rectal). The physical findings did not change appreciably during this period except for increased intensity of the icterus which then appeared to clear, the icteric index reaching 35 and then falling to 14 on the sixth day; the W.B.C. rose to 31,000. At 4:00 A.M. the morning of the seventh day, the patient suddenly expired. Necropsy revealed generalized acute bile peritonitis secondary to a small perforation 1 mm. in diameter in the common bile duct which was situated 3.5 cm. below the cystic duct stump. The common bile duct was markedly distended and at a little distance below the perforation contained a single faceted cholesterol stone 1.4 cm. in diameter. At the level of the stone the common duct wall was thicker than elsewhere. The diverticulum of the common duct said to have been observed at the last operation was not found.

CASE 2.—M. S., a woman aged 72 years was admitted to Billings Hospital Dec. 22, 1942. Since 1939, there had been attacks of right upper quadrant pain radiating to the back and shoulders, with nausea, vomiting, and transitory icterus. Cholecystectomy was done in 1941, and following this there was freedom from attacks. Three days prior to the present admission severe pain developed in the right upper quadrant and radiated to the left shoulder. Nausea and vomiting were frequent and icterus developed. On physical examination there was diffuse abdominal tenderness with muscle spasm in the right upper quadrant. Temperature was 102.8° F. (rectal); W.B.C., 19,800; Icteric index, 47; B.P., 130/70; pulse, 120. During the next three days the general asthenic condition of the patient improved slightly, nothing having been permitted by mouth and a total of 3000 c.c. of dextrose and saline solution being given daily parenterally. At the end of this period the abdominal rigidity was sharply localized to the upper right quadrant where a deep abscess seemed to have formed (fluctuation). The remainder of the abdomen was

flaccid and only slightly tender. Laparotomy was performed by excision of the old upper right rectus incision scar, and the deeper layers of the abdominal wall were observed to be edematous and bile stained. When the peritoneum was incised dark green, thick purulent fluid escaped from a cavity lined by fibrinous exudate. This cavity was observed to be a large pocket below the right lobe of the liver anterior to the porta hepatis. When all purulent material had been cleaned out, the common duct, about 2 cm. in diameter, was observed at the bottom of the pocket, and at a point about 2 cm. above the upper margin of the duodenal curvature there was an oval perforation about 1.5 cm. in diameter. The index finger was inserted into the common duct in both directions and distally behind the duodenum an oval concretion about 1.5 cm. in diameter was palpated. This was lifted out through the perforation in the common duct. Probing in both directions

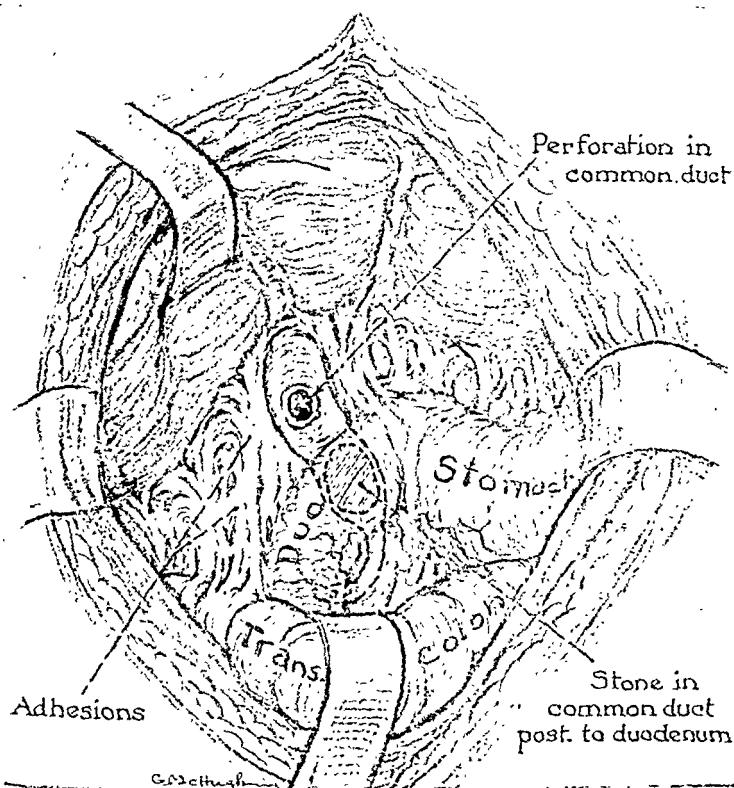


Fig. 1.—Showing findings at laparotomy in Case 2. Large pocket exposed through incision of abdominal wall was filled with bile and purulent exudate; large oval perforation was present in common duct. Concretion in lower common duct was somewhat impacted in position shown. Findings suggest rupture due to hydrostatic pressure above concretion. Recovery followed stormy convalescence.

failed to bring up other stones. A probe was passed into the duodenum via the common duct and ampulla without encountering obstruction. A catheter was inserted into the perforation and the latter closed by interrupted sutures about it. There was no visible evidence of cystic duct stump. Penrose drains were inserted into the depths of the large pocket and the abdominal wound closed. Final diagnosis: Localized upper abdominal bile peritonitis secondary to ruptured common duct,

choledocholithiasis. After a convalescence characterized by periods of marked asthenia and mental disorientation, the patient's icterus had cleared by the thirty-seventh postoperative day and stools contained bile. The small biliary fistula healed. The general condition improved markedly, and the patient was discharged from the hospital. Three months after the operation, the patient was well.

#### DISCUSSION

The cause of rupture of the common duct has been variously stated as due to one or a combination of factors which include: (a) increased intraluminal pressure from obstruction below the point of rupture, (b) necrosis of a portion of the common duct wall secondary to thrombosis of mural vessels, (c) necrosis of the duct wall secondary to pressure from impacted stone, (d) infection, (e) slough of the cystic duct stump, (f) rupture of a weak segment of duct wall, such a vulnerable point resulting from common duct drainage. Where extensive changes in the extrahepatic biliary duct walls are not present, and in the absence of stones, the pathogenesis of rupture is obscure. Needless to emphasize again, postcholecystectomy rupture of the common duct is another of the unfortunate sequelae of overlooked common or hepatic duct stones at the time of cholecystectomy. It is of interest to note that in both of the cases reported above the perforations in the common duct were *above* a large stone, and that judged from necropsy and findings at operation these perforations could hardly be ascribed to direct pressure necrosis from the concretions.

The syndrome of upper abdominal pain, becoming quite severe, upper and later general abdominal tenderness and rigidity, elevation in temperature, marked leucocytosis, rapid pulse, varying degrees of general collapse and icterus (after a few days) in a patient who previously has undergone cholecystectomy for cholelithiasis and cholecystitis should strongly suggest perforation of the common bile duct with extravasation of bile and bile peritonitis.

Differential diagnosis from biliary colic due only to common duct stone or stone in the ampulla should not be difficult since in the latter event the clinical evidence of peritonitis will not be present, and general collapse will not have developed. Differential diagnosis from carcinoma of the ampulla or head of the pancreas will be readily apparent also, because of the absence of evidence of peritonitis. Severe diffuse cholangitis of sudden onset might afford some early difficulty in differentiation, but as the hours pass, lack of evidence of peritonitis will preclude the diagnosis of ruptured common duct.

The almost certain fatal outcome of this condition if laparotomy is not performed justifies laparotomy at the earliest moment when the diagnosis appears probable. Evacuation of the extravasated bile, drainage of the upper abdomen, and drainage of the common duct will afford the only opportunity for survival. While in the recorded experience the mortality following this procedure under these circum-

stances has been very high, it would, nevertheless, appear to be primarily the mortality of the disease. A more general appreciation of this late complication of cholecystectomy for biliary lithiasis might entail earlier operation with possibly a greater incidence of survival.

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## MANAGEMENT OF THE APPENDICAL STUMP

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THERE are four reasons why this study was undertaken: (1) In spite of the fact that fifty-nine years have passed since Krönlein<sup>1</sup> in 1884, performed the first appendectomy, there is still no generally accepted technique for the management of the appendical stump. (2) Severe complications due to massive leaking of abscess of fecal material at the stump area are still being reported in the surgical literature and it is quite likely that this catastrophe occurs much more often than is indicated by these reports. (3) The occasional stormy postoperative course of an interval or incidental appendectomy and the occasional finding of many unexpected adhesions in the right lower quadrant when the abdomen is reopened, may well be due to slight unrecognized leaking of the stump area after the previous appendectomy. (4) Probably the real reason for the study lies in the fact that the authors, after trying most of the accepted methods of handling the appendical stump, were never completely satisfied with any method which they tried.

Eleven years after the first appendectomy, Dawbarn,<sup>2</sup> in 1895, mentioned eleven different methods of treating the appendical stump and then described a new method of his own. It is interesting to consider some of the methods that Dawbarn mentioned. They include amputation of the appendix flush with the cecum and closure of the hole by one or two rows of Lembert sutures; ligation and cauterization of the stump with the cauterization being performed either before or after ligation; ligation, cauterization, and inversion of the stump by Lembert sutures; cauterization of an unligated stump with inversion beneath two rows of Lembert sutures; inversion of a tied, cauterized, half-inch long stump concealing the suture line under omental or mesenteric peritoneum; inverting the entire unopened appendix into the cecum; amputation between clamps leaving the clamp on the stump for a day or two; and finally, doing nothing to the appendix if its removal seemed likely to spread infection.

The plan advocated by Dawbarn called for a purse-string suture one-fourth of an inch from the appendix, the appendix divided leaving a stump never shorter than one-half an inch, the lumen of the appendix to be stretched by the introduction of a pair of closed mouse-tooth forceps through the appendix into the lumen of the cecum "then gently opening the blades—thereby any stricture, from swelling or plastic deposit, will be stretched." Lastly, the untied stump of the appendix

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was to be invaginated into the cecum as the purse-string suture was tightened and tied.

By 1904, Seelig<sup>3</sup> was able to state that "in general the methods of treating the stump of the appendix may be grouped under three heads, as follows (Fig. 1, *I*, *II*, and *III*).

"(a) Ligation of the base of the appendix, ablation of the organ distally to the ligatures, and inversion of the stump by means of Lembert sutures passed through the peritoneum of the cecum. In these cases the appendical stump is inverted into the wall of the cecum.

"(b) Ablation of the organ without previous ligation of its base, and inversion of the stump into the lumen of the cecum; Lembert sutures over the site of inversion.

"(c) Simple ligation, ablation of the organ distally to the ligature, and cauterization of the stump. The disinfected stump is dropped back into the peritoneal cavity."

In 1937, Ochsner and Lilly<sup>4</sup> reviewed the question from the standpoint of the same three basic methods: (1) simple ligation of stump; (2) ligation and inversion of the stump into the cecal wall; and (3) inversion of the unligated stump into the lumen of the cecum. Their experience with three instances of stump leakage following the first two methods led them to consider inversion of the unligated stump the method of choice.

There are two objections to the simple "tie and drop" method of handling the appendical stump. The objection most often mentioned is the absence of serosa-to-serosa apposition when the appendix is ligated with or without preliminary crushing. If the tight tie or crushing severs the mucosa and the pulpy lymphoid tissue, the tie then brings submucosa to submucosa and not serosa to serosa. While this is important, it is not as important as the other objection to this simple ligation technique. This second objection lies in the fact that the stump of the appendix not only sloughs distal to the tie but also sloughs at the point of the tie. In fact no healing takes place until this slough is removed. If a dog's abdomen is opened four or five days after its appendix has been tied with 0 chromic catgut and the carbolized stump dropped back into the abdominal cavity, the operator will see a mass of fibrinous adhesions joining ileum or omentum to the stump area. If these are carefully separated, either an opening into the cecum will be found or the site of the appendical stump will be closed by a very thin layer that looks like a spider web. If, on the fourth or fifth postoperative day, the adhesions about the stump are not separated but the cecum is squeezed gently, fecal material can be seen escaping from the insecurely healed stump. This finding was noted in the five animals treated by the simple "tie and drop" method. It seems that from the moment the appendix is tied a race is started between the protective adhesions which tend to cover and seal off the necrosing stump and the anemic necrosis

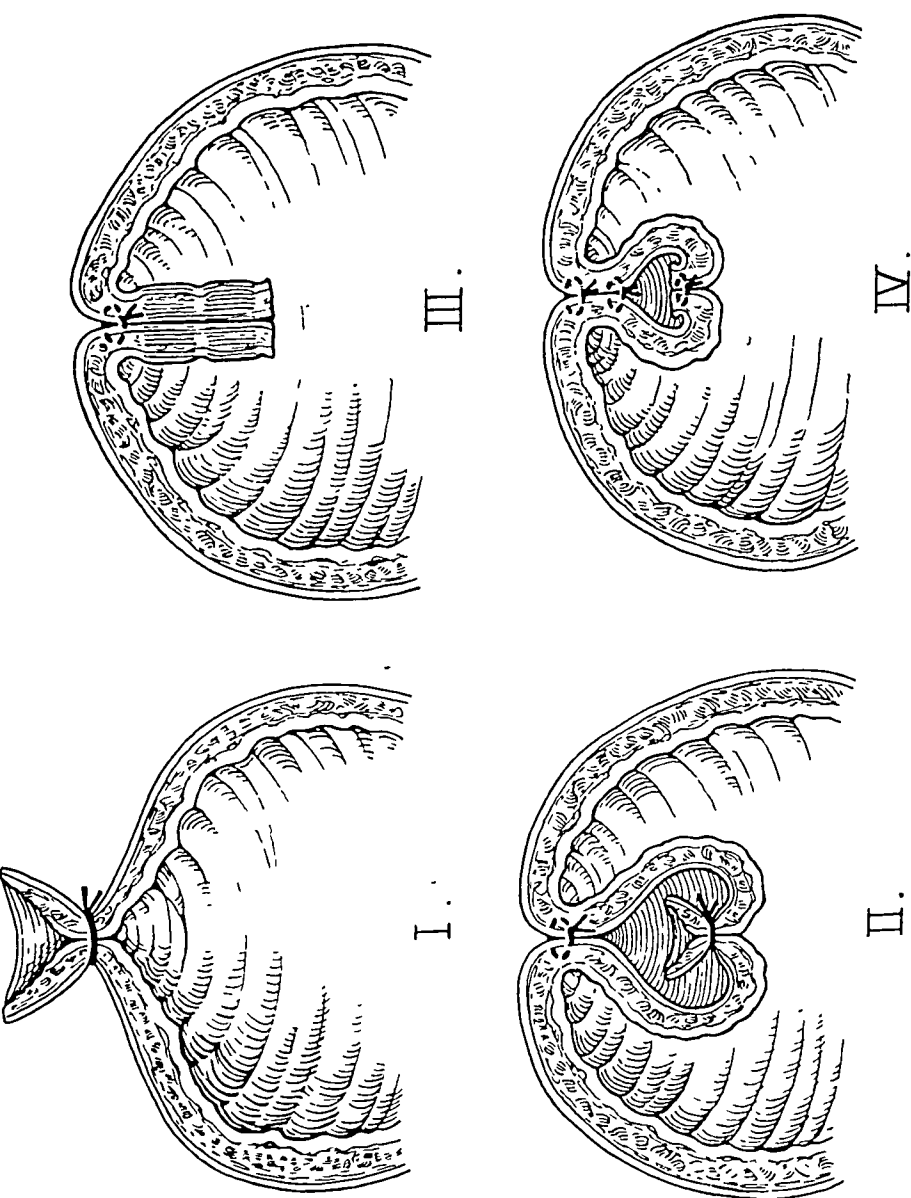


FIG. 1.—I, Simple ligation of stump; II, inversion of tied stump; III, inversion of unligated stump; IV, inversion of small stump made possible by the use of a catgut pursestring instead of a tie about the base of the appendix.



at the point of the tie which tends to slough into the lumen of the cecum. It may be that the mucosa, severed by the tie or crushing, grows over the opening in the cecal wall and saves the day, but the cecal wall cannot start healing until it first sloughs through. This means that for a few days there is a distinctly weak area in the cecal wall. In the experimental animals examined three weeks after operation only a few adhesions were evident but the cecal wall showed no evidence of weakness. That the race is usually won by the defense mechanisms is attested to by the fact that so many appendectomies are successfully handled by this technique. However, there is little doubt but that there is a period of great danger at some point probably about the third or fourth day, when the appendical stump is partly sloughed away and when the defenses are still fibrinous. Marked distention, straining, or a "high" enema during this period could well cause the filmy covering of the stump to give way, allowing either a small or possibly a large cecal leak. This series of events might explain the occasional unexpected thickening of adhesions about the cecum and ileum in a case that had had an incidental appendectomy or interval appendectomy but a stormy postoperative course.

The inversion of the unligated stump method produces the highly desirable serosa-to-serosa apposition of the stump which is turned into the cecum. It also produces no pocket in the cecal wall as the end of the stump is pushed into the lumen of the cecum. Four dogs were operated upon by this technique. On the fourth or fifth day, reoperation showed the best healing of any of the experiments with little or no adhesions on the outside and but slight sloughing evident on the inside. If this inversion could be made safely there would be no question about this being the method of choice. The difficulty lies in the anatomic fact that the wall of the appendix is so thick in comparison with the small diameter of its lumen. This state of affairs makes complete inversion of the untied appendical stump into the cecum difficult and at times impossible. It should be remembered that Dawbarn, the originator of this technique, advised stretching the lumen of the appendix with a forceps introduced through the stump into the cecum before attempting inversion of the stump. Many ingenious methods<sup>4,7</sup> of inverting the untied appendical stump into the cecal lumen have been described but they have two objectionable features. One is the possibility that the unligated stump is not inverted, but merely pushed down into the cecal wall, and the other, the danger of soiling the field as the unligated stump is forced in on itself into the lumen of the cecum. If an assistant squeezes the cecum too tightly, if a narrow forceps or clamp does not completely close the end of the stump as it is being inverted, or if the purse-string suture should break before the stump was completely turned in on itself, soiling is possible. The question of hemorrhage from the unligated appendical artery has often been mentioned as a danger

of this technique. This danger seems more theoretical than real. It is recognized that a trained operating team can invert the unligated appendix stump with no soiling, but the technique can become difficult and if the members of the team are unfamiliar with the dangers of the technique, soiling is possible. For this reason inversion of the unligated stump of the appendix does not seem to be the safest method of handling this problem.

Inversion of the tied appendical stump avoids the danger of soiling during inversion but carries with it the objectionable feature of producing a pocket in the cecal wall, a pocket that contains the necrotic appendical stump caught between the catgut tie below and the silk or cotton purse string above. Using eight dogs, appendectomy was done by this technique; the tie was of 00 chromic catgut and the purse string of quilting cotton. Reoperation on the fourth or fifth day revealed adhesions about the stump area that were more abundant than those found after inversion of the unligated stump technique but much less than was found after the simple ligation experiments. In no instance could fecal material be squeezed out of the imperfectly healed stump area. Four animals were reoperated upon on the twentieth postoperative day. The only noteworthy finding at that time was the reduction in size of the inverted stump when viewed from within the cecum. The stump had probably sloughed off and drained into the cecum because all that was left was a small nubbin 7 mm. in diameter and projecting into the lumen about 1 or 2 mm. Microscopic examination of the stump areas removed on the fourth postoperative day showed necrotic tissue and abscess formation in every instance but there was little spread of the inflammatory reaction into the cecal wall that formed the sides of the pocket. This tends to discredit the objection to a purse-string suture on the grounds that it devitalizes the cecal wall and makes the wall subject to invasion of infecting agents. The observation that the intact serosa checks the spread of inflammation into the cecal wall further suggests that the serosa of the appendical stump and cecal wall should be left intact and not crushed nor incised and crushed before ligation, if the stump is to be inverted. Some slides showed the pocket abscess extending dangerously close to the cotton purse-string suture. It seemed that a second purse string which would turn in a little more serosa would add materially to the safety of the procedure.

It was evident that here again a race was in progress. A race between the holding properties of the purse string above and the catgut tie below, with the pace determined by the enlarging abscess between the two, since it was very evident from these specimens and sections that the size of the inverted stump determines the size of the resulting abscess. It follows, therefore, that any reduction in the size of the inverted stump would reduce the size of the cecal pocket abscess. The smaller abscess should slow the tempo of the race and by slowing the race, favor the cotton

purse string which can stand time better than can the catgut tie. If an operator tries to achieve this end by cutting closer and closer to a catgut tie, the tie is likely to be pulled off during the subsequent carbolization of the stump. If, however, instead of a tie, a purse-string suture of catgut is placed at the very base of the appendix and tied tightly, the appendix can be cut off flush with this suture (Fig. 1, IV). This reduces to a minimum the amount of tissue turned into the cecal wall and thus should tend to reduce the size of the cecal wall abscess.

Experiments were carried out on eight dogs employing this double purse string rather than the catgut tie and cotton purse string technique (Fig. 1, IV). On the fourth or fifth day, reoperation revealed little or no reaction about the site of inversion. It looked about the same as the stump area following the inversion of an unligated stump. This means there was less reaction than was found after the ligation and inversion technique and, of course, much less reaction than found after the "tie and drop" technique. In four instances, sections made through the cecal pocket area found following the inversion of the small stump showed a subacute inflammatory reaction rather than an abscess (Fig. 2). In some sections the reaction was certainly not enough to be called an abscess since it showed only granulation tissue. Four animals were reoperated upon on the twentieth postoperative day. The outer surface of the cecum showed very few adhesions and the inner surface showed only a tiny elevated area 4 mm. in diameter.

This technique is applied to the human appendix in the following manner. A Kelly clamp is applied to the distal end of the meso-appendix, the peritoneum of the lateral side of the meso-appendix is incised if the meso-appendix is thick, or if the appendix is angulated in its mid-portion. This allows the entire appendix to be delivered from the depths of the wound and also allows the operator to see and doubly clamp only the vessels of the meso-appendix. After the vessels are divided the clamps on the mesoappendix are replaced by silk or cotton ties and usually a suture is tied about a small artery found in the angle between the appendix and the part of the cecal wall covered by the meso-appendix. Division of this artery mobilizes the cecum in the region of the base of the appendix and also reduces the likelihood of hematoma formation during the placing of the various purse-string sutures. The first purse string is placed exactly at the base of the appendix and is of 00 plain or 00 chromic catgut on a straight intestinal needle. If the base of the appendix is deep in the wound due to a fixed cecum, this purse string can best be placed with very fine curved French or split-eye needle. The bites of the catgut purse string should be as small as possible and should include only the serosa and part of the muscularis of the appendix. Usually only four or five bites need be taken in placing this purse string. As soon as the purse string is placed it is tied tightly and the ends of the suture cut. The usual purse string of

cotton or medium silk is next placed in the cecal wall about the base of the appendix. It is desirable, however, to place this purse string closer to the base of the appendix than would be possible if a large stump were to be inverted. An Ochsner clamp is then placed immediately



Fig. 2—A. Section through stump area taken on fourth postoperative day following inversion of tied catgut purse-string technique. B. Section through stump area taken on fourth postoperative day following inversion of tied catgut purse-string technique.

distal to the tied catgut purse-string suture. After it has crushed the appendix for a moment or so it is removed and a small straight clamp is applied to the distal part of the groove left by the heavy Ochsner clamp and the appendix is then amputated as close to the catgut purse-string suture as possible. This method of amputating the appendix

prevents soiling as the amputation is carried out through the dry crushed groove left by the Ochsner clamp; it also results in a minimal amount of appendical stump left to be turned in. After the small flat stump has been treated with phenol and alcohol, it is easily inverted by the cotton purse-string suture in the cecal wall. The procedure is completed by the insertion of either a mattress suture or a small three or four bite purse-string suture of cotton that picks up only a seromuscular bite and tends to turn in a little more peritoneum at the critical point of stump inversion.

An objection might be raised to the many stitches taken in the cecum by this triple purse-string method of handling the appendical stump. However, the stitches of the catgut purse string are quite safe because they are placed in the serosa and muscularis of the relatively thick-walled appendix. The outermost suture is safe because it also engages only the serosa and muscularis. The middle cotton or silk purse string which engages a few fibers of the submucosa is a dangerous suture if it is placed with a large needle and especially if this needle is a curved needle held in a needle holder. If, however, a fine straight needle such as a No. 8 Warwick Castle Milliner's needle and quilting cotton or medium silk thread is used, it is possible to place this middle purse-string suture safely. This view is supported by the fact that when the needle and what was left of the cotton thread after the purse string had been tied were cultured in fifteen instances and there were no positive cultures.

#### CONCLUSIONS

The fate of the appendical stump has been studied in the dog. Apparently, the size of the tied inverted stump determines the size of the resulting cecal pocket abscess which is the chief objection to the inversion of a tied appendical stump. The substitution of a catgut purse string for the usual catgut tie about the base of the appendix allows amputation of the appendix flush with this catgut purse-string suture, thus reducing to a minimum the amount of appendical stump to be inverted.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## STUDIES OF THE CIRCULATION IN CLINICAL SHOCK

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### INTRODUCTION

THE investigation reported in this and subsequent papers is a study of the circulation in various types of injury as met with in the admitting emergency service of Bellevue Hospital, New York. A considerable proportion of these cases showed in varying degree the manifestations of shock, and the primary purpose of the work has been to describe the circulatory changes in shock in human subjects.

The physiologic measurements have been chosen so as to make this description of the circulation as comprehensive as possible. Specifically, the major functions of the general systemic circulation which have been measured in each subject are:

1. Intravascular pressures, in femoral artery, median basilic vein, and the right auricle.
2. Plasma volume, by the dye technique of Gregersen; red cell and total blood volume (using hematocrit values); plasma protein.
3. Cardiac output, by "direct Fick" technique.
4. Pulmonary ventilation, respiratory gas exchange.

In addition, the circulation through one organ, the kidneys, has been measured in a number of cases, by the clearance techniques of Smith.

Of these measurements, the intra-auricular pressure and the "direct Fick" cardiac output, achieved through direct catheterization of the right auricle, and the renal clearances have not previously been reported in the investigation of traumatic shock in man.

The work described in this paper was done under a Committee on Medical Research, between the Office of Development, and Columbia University, with the collaboration of the Josiah Macy Foundation. Additional support for the research was provided by the

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The clinical material that has been available to us, while varied, has also been in many respects quite limited. We have seen a number of cases of skeletal trauma, especially multiple fractures, several head injuries, burns, hemorrhages, and abdominal injuries. On the other hand, chest injuries have been few and we have had but one case of gunshot wound, no stab wounds, or wounds with extensive loss of muscle substance. Also, most cases were seen soon after injury so that the effects of exposure, dehydration, etc. were rarely encountered. The age distribution was wide; while many patients were in the older age groups, a number were young and had been in excellent physical condition before injury. Acute alcoholism was a complicating factor in several instances.

In the presentation of data, consideration will be given both to combined or average results in various types of injury, and to particular results in special individual cases. Average values show trends and thus define the general pattern of the condition that is under study. The exceptional case is often blotted out in the average. We believe that our techniques are both sufficiently comprehensive and sufficiently reliable so that the data of the single case study are significant. Individual responses to injury, though they may be exceptional within small groups of cases such as have been available to us in the present investigation, may be of great importance from the point of view of the mechanism of shock.

For example, it is important to know that, in a group of cases, there is a large decrease in the average figure for circulating blood volume. It is of equal importance to know whether, in specific instances, the state of shock *can* develop *without* extensive loss of blood volume.

The present paper will include the following:

1. Description of procedure and of the various methods of measurement employed, with critical comments concerning some of these methods.
2. Description of the state of circulation in various types of injury, both with and without shock, on the basis of average results in thirty-six cases.
3. Changes in the circulation occurring during recovery from shock, on the basis of average figures in six cases.
4. The state of the renal circulation in relation to shock.

In subsequent papers, a number of individual cases will be described, illustrating not only particular states of shock, but also various forms of progressive change occurring during the periods of observation, the latter lasting sometimes a few hours, sometimes several days. Data will also be presented showing the changes in blood volume produced by administration of fluids, blood, plasma, and saline; serum electrolytes in certain cases of shock; types of arterial and of right ventricular pressure curves obtained by an optical registration method; additional observations on renal clearances; and the effects of certain drugs.

The research has been in many respects a cooperative effort. Much of the original plan of the work was due to Lt. Col. Frank B. Berry, at that time director of surgery on the Tuberculosis Service of Bellevue Hospital. Col. Berry was also of great assistance, subsequently, in putting the plan into effect.

The investigation was made practicable through the action of the Bellevue Hospital Medical Board, making available all of the admission facilities of the Hospital.

In carrying out the research work itself, three groups of investigators have collaborated: one group under Richards and Courmand of the department of medicine, College of Physicians and Surgeons, responsible for general hemodynamics and respiratory studies; a group under Gregersen of the department of physiology, College of Physicians and Surgeons, responsible for blood volume studies, and a group under Dr. Smith, of the department of physiology, New York University College of Medicine, responsible for arterial pressure recording, and for studies of renal function.

#### PROCEDURE

Each patient was seen as soon as possible after admission by a member of the research group, and a consultation held with the surgeon in charge. An evaluation of the clinical signs and symptoms was made, and if the case was considered suitable, the investigative studies were then started immediately. An attempt was made to obtain the first series of measurements before any treatment had been instituted.

The patient was weighed by suspending him from a hanging scale by means of ropes attached to the four corners of a canvas stretcher. His height was determined with a measuring tape. To facilitate fluoroscopy, he was placed on a special fracture bed of which the mattress and springs were replaced by tightly drawn canvas straps. Catheterization of the right auricle of the heart, under fluoroscopic control, was then performed; the catheter's position was further established by anteroposterior and lateral x-rays. While this was being done, a 19 gauge Ungar needle, with tight-fitting obturator,\* was introduced into a femoral artery and another into a peripheral vein, and left in place throughout the series of measurements. Both auricular catheter and venous needle were kept patent by a slow continuous flow of saline solution. The determination of blood volume was begun. Simultaneous readings of auricular pressure and peripheral venous pressure were taken, and intra-arterial pulse tracings were recorded optically from the femoral artery, by Hamilton's method. Samples of blood and expired air, for cardiac output determination by the direct Fick method, were then taken, followed by another arterial pressure tracing and (in earlier cases) by a ballistocardiographic tracing. Finally, glomerular filtration and plasma flow through the kidneys were studied by clearance techniques.

\*Specially designed and provided through the courtesy of Ecton, Dickinson and Co



Clinical signs and symptoms and any changes in the patient's condition were noted in the protocol. All medication and fluids were also noted, and the amount of blood withdrawn was recorded, and that otherwise lost was estimated when possible. Roentgenograms were taken to record the position of the catheter in the heart.

The whole series of studies was repeated at intervals before and after therapy when this could be done without interfering with the clinical management of the case.

#### METHODS

*Plasma Volume, Serum Protein, and Hematocrit.*—Determinations of the plasma volume were made with the T-1824 method (Gregersen and co-workers<sup>1</sup>). Depending upon the weight of the patient, 4 or 5 c.c. of 0.4 per cent dye were injected into the peripheral venous needle with a calibrated 5 c.c. syringe. If repeated withdrawal of venous blood for the purpose of rinsing the syringe became difficult, rinsing was done with saline solution from a reservoir connected to the needle with a watertight three-way stopcock. The dye-free control sample and subsequent dye-tinged samples (collected at 5-minute intervals during the first half hour, and then at 10-minute intervals) were drawn from the arterial needle. The blood was placed in oiled tubes and the concentration of dye (expressed as optical density) in each serum sample was determined with a Koenig-Martens visual spectrophotometer (Gregersen<sup>2</sup>). The plasma volume was calculated from the equation:

$$\text{Plasma volume in c.c.} = \frac{\text{c.c. dye injected} \times 250 \times K}{C_0}$$

in which  $K$  is the optical density of the dye solution diluted 1:250 in serum, and  $C_0$  is the initial dye concentration (expressed as optical density) derived by extrapolation of the dye curve on a semilog plot (Gregersen and Rawson, in press). As described elsewhere, the effects of fluid shifts on the dye curve were always considered in the final analysis of the data (Gregersen and Noble, to be published).

The serum protein values reported in the tables of results were determined with the falling drop method (Barbour and Hamilton<sup>3</sup>), the formula of Weech, Reeves, and Goettsch<sup>4</sup> being used for conversion of serum specific gravity to serum protein content. Hematocrit values were obtained on arterial samples using 1 c.c. Wintrobe tubes and crystalline heparin as anticoagulant, after 40 minutes' centrifugation at 2,500 r.p.m.

The total blood volume was calculated from the plasma volume and the arterial hematocrit according to the formula:

$$\text{Total blood volume in c.c.} = \frac{\text{plasma volume in c.c.}}{100 - \text{hematocrit } \%} \cdot 100$$

The value so obtained is higher than the true blood volume because

the per cent cells obtained by centrifugation includes a small amount of plasma trapped in the cell mass (Gregersen and Schiro) and because the per cent erythrocytes in the blood from large vessels is higher than the body hematocrit.<sup>5-8</sup> Nevertheless, the calculation is appropriate for the present purpose since we are comparing the results with average normal values derived in the same manner. Discussion of this question will be found in a separate paper which deals with the mixing time and disappearance rate of T-1824 in human cases of shock, and with the evidence that this dye measures the plasma volume in shock. It may be stated here, however, that evidence of increased capillary leakage was not found in cases of shock from skeletal trauma or hemorrhage. The dye disappearance rates were approximately the same during shock as after recovery.

*Catheterization of the Right Heart. Auricular and Venous Pressures.*—The catheterization of the right auricle was carried out by cutting down on a median basilic vein of either right or left arm, and running in a No. 8 or No. 9 ureteral catheter,<sup>\*</sup> according to the technique of Cournand and associates.<sup>9</sup> Continued experience with this procedure has proved its safety, no unfavorable complications having arisen in over 150 catheterizations, beyond occasional linear mural thrombosis near the site of the incision. The catheter has been left in place continuously for as long as twenty-four hours. It was frequently most useful as a means of administering blood or other fluids.

Auricular pressure readings were taken by the use of a saline manometer,<sup>10</sup> and peripheral venous pressures recorded in the same manner, on a second manometer. The levels of venous and auricular pressures were recorded, using as the zero point the position of the tip of the catheter in the right auricle (established by lateral x-ray).<sup>10</sup>

The average vertical distance in thirty cases, from the angle of Louis on the external surface of the chest to the tip of the catheter in the right auricle, was 66 mm., S.D.  $\pm$  13.

The true criterion of adequacy of return of venous blood to the right heart is the "effective pressure" in the right auricle; that is, the mean right auricular pressure relative to the atmospheric pressure, plus the amount of the mean negative intrathoracic pressure as it exists in the region of the right auricle. There are two respects in which the auricular pressure, as measured by our technique, deviates from this ideal value.

One hydrostatic element that may be somewhat variable is the depth of the chamber constituting the right auricle. The catheter, according to x-ray evidence, lies almost always along the dorsal wall of the auricle. A deep right auricle would give a somewhat higher level of pressure, as recorded on the manometer, than a shallow one. It is possible that

<sup>\*</sup>Specially designed and provided through the courtesy of the United States Catheter and Instrument Corp., Glens Falls, N. Y.

a poor venous return might result in some flattening of the antero-posterior diameter of the auricle, with the patient lying supine. As a source of error of mean auricular pressure, however, this factor is probably not large.

More important is the pleural pressure. Abnormal breathing may produce changes in either direction. With hyperventilation, however, the pleural pressure usually becomes more negative, especially if the breathing is asthmatic or stertorous. This means that the effective pressure at the right auricle will be larger, for the same (atmospheric) level of the right auricular pressure. A further source of error is that with this type of breathing, the auricular pressure as recorded is usually nearer the inspiratory level, since saline solution is sucked out of the long catheter more readily than blood is forced back in.<sup>10</sup> If the breathing is unimpeded, however, and relatively quiet, it is probable that auricular pressure levels can be compared with normal values, and that changes occurring in the clinical course of the individual case will represent corresponding changes in effective venous return.

*Arterial Blood Pressure.*—Arterial pressure was measured in the femoral artery by a Hamilton optical manometer,<sup>11</sup> mean pressure being determined by planimetric integration of the area under the pressure pulse curve.

*Cardiac Output by the "Direct Fick" Method.*—The direct Fick determination<sup>9</sup> of cardiac output requires simultaneous sampling of mixed venous blood, arterial blood, and expired air.

After flushing out the saline solution in the catheter by withdrawing 5 to 10 c.c. of blood back through it, a 15 c.c. sample of mixed venous blood was then taken under 5 c.c. of oil in a syringe. Air contamination was excluded by a tight rubber adapter and a Luer-lock connection. Arterial blood was similarly collected in an oil syringe attached directly to the indwelling arterial needle. Both samples were immediately transferred to iced blood bottles containing 10 c.c. of oil, previously boiled to remove the air, and crystals of anticoagulant (.06 mg. sodium fluoride and 4.5 mg. neutral potassium oxalate dried in autoclave). They were stirred slowly to prevent settling of red blood cells, taken directly to the laboratory, and analyzed immediately for oxygen and carbon dioxide.

Expired air was collected and measured in a Tissot spirometer or Douglas bag. A rubber mouthpiece and noseclip were usually found satisfactory, but it was frequently found necessary to hold the patient's lips tightly around the mouthpiece. Occasionally in an unconscious patient who required a metal pharyngeal airway, an anesthesia mask was used and care taken to avoid leaks. The spirometer or Douglas bag had been flushed out with expired air a few minutes before the expired air sample was taken for analysis.

Expired air was collected over an accurately measured interval, from 1 to 2 minutes. Fifteen seconds after the start of the expired air col-

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Expired air was collected over an accurately measured interval, from 1 to 2 minutes. Fifteen seconds after the start of the expired air col-

lection, mixed venous blood sampling was begun, followed 15 seconds later by arterial blood sampling. Each blood sample required about 25 seconds to collect and so was spread out over a considerable part of the air-sampling period. The pulse was counted throughout the sampling procedures.

Carbon dioxide and oxygen contents of mixed venous and arterial blood were done in duplicate on the Van Slyke-Neill apparatus. Expired air samples were analyzed in the Haldane apparatus to determine oxygen intake and carbon dioxide output per minute.

According to the Fick equation:

$$\text{Cardiac output (l./min.)} = \frac{\text{O}_2 \text{ intake (c.c./min.)}}{\text{O}_2 \text{ arteriovenous diff. (c.c./l. blood)}}$$

or

$$\text{Cardiac output (l./min.)} = \frac{\text{CO}_2 \text{ output (c.c./min.)}}{\text{CO}_2 \text{ arteriovenous diff. (c.c./l. blood)}}$$

Cardiac output was calculated independently from the carbon dioxide and from the oxygen data, and the average value taken. Cardiac index in l. per min. per square millimeter body surface and stroke volume in cubic centimeters per beat were also calculated.

A brief comment upon the validity of this method follows:

TABLE I

VALUES OF OXYGEN AND CARBON DIOXIDE IN SUCCESSIVE SAMPLES OF MIXED VENOUS (RIGHT AURICLE) BLOOD

PATIENT	CO <sub>2</sub> CONTENT, VOL. PER CENT		O <sub>2</sub> CONTENT, VOL. PER CENT	
	(1)	(2)	(1)	(2)
F. C.	56.2	55.4	11.2	11.2
G. B.	54.1	53.9	3.9	4.1
T.	54.5	55.4	5.9	6.3
D.	54.0	55.6	6.8	7.3
F. K.	57.2	57.4	12.4	12.9
W. D.	52.5	52.8	--	--
M. W.	--	--	12.0	11.8
Y. C.	54.4	54.9	12.8	13.0
O. K.	50.6	50.2	10.5	10.0
T. C.	47.6	47.4	10.6	10.4
V.	57.0	53.8	13.6	14.1
D. J.	41.6	42.7	11.3	11.3

*Mixed venous blood sample:* The most important question is whether the sample of blood taken from the right auricle can be relied upon to represent true mixed venous blood. The best evidences that we have at present on this point are: (1) A series of eleven patients, from each of whom repeated samples were taken within a few minutes' time, with the subject in an apparently steady state (Table I). It will be seen that values of mixed venous oxygen remained fairly steady; there were no differences between successive samples larger than 0.5 volume per cent. The agreement in the CO<sub>2</sub> values was not as good. (2) A series of ten patients (all but one being normal subjects, or subjects with

arterial hypertension), from each of whom samples from the right ventricle and right auricle were drawn within a few minutes' time. The average difference in O<sub>2</sub> content between the two samples was .11 vol. per cent, the largest difference being .3 vol. per cent. The carbon dioxide contents were not as constant, the average difference being .63 vol. per cent, the largest 2.1 vol. per cent. In four cases of this series a second auricular sample was taken immediately after the first, after the tip of the catheter had been withdrawn further into the auricle, nearer to the superior vena cava; in two instances the O<sub>2</sub> content of both auricular samples checked within .1 vol. per cent; in the other two a rather large discrepancy was noted, amounting to .9 and 1.1 vol. per cent respectively. Although these observations are still too few, they suggest that in normal subjects the oxygen content of the auricular blood is the true "mixed venous" oxygen, providing that the tip of the auricular catheter is accurately located close to the tricuspid valve.

TABLE II

COMPARISON OF CARDIAC OUTPUT CALCULATED BY THE DIRECT FICK METHOD  
AND BY THE BALLISTOCARDIOGRAM

PA- TIENT	CONDITION	TOTAL BLOOD VOLUME (C.C. PER SQ. M. B. S.*)	HEMA- TOCRIT (%)	CARDIAC OUTPUT		
				FICK (L. PER MIN. PER SQ. M. B. S.)	BCG. (L. PER MIN. PER SQ. M. B. S.)	DIFFER- ENCE $\frac{CO_F - CO_B}{CO_F} \times 100$
J. H.	Head injury, coma	2850	43	3.02	2.69	+10.8
J. L.	Skeletal trauma, no shock	2260	41	3.08	3.12	-1.4
S. V.	Skeletal trauma, no shock	3860	43	4.15	3.77	+9.2
A. V. H.	Recovery from burns	2760	37	3.91	3.49	-10.7
J. E.	Recovery from hemorrhage	3310	37	4.15	4.34	+1.8
E. C.	Recovery from hemorrhage	3110	25	3.21	2.15	+24.5
J. E.	Severe hemorrhage	2070	38	2.99	5.04	-55.6
E. C.	Severe hemorrhage	2290	24	2.45	3.30	-40.5
E. C.	Further bleeding	2120	18	2.46	4.28	-71.5
McN.	Skeletal trauma, mild shock	1900	25	2.56	3.10	-20.8
M. C.	Skeletal trauma, milk shock	2195	34	2.18	3.79	-73.9
Y. T.	Burns, mild shock	2272	58	1.62	1.70	-4.9

\*Cubic centimeter per square meter of body surface

*Arterial blood:* This is a reliable sample. The arterial needle remains in place throughout the series of measurements, and there is thus no pain at the time the arterial blood sample is taken.

*Expired air:* It may well be argued that a 1-minute sample is too short and it is true that there may be some error due to this. Patients in shock, however, are often restless and a longer period of collection of expired air may result in struggling or other effort which produces a still greater error.

The figures for cardiac output in this report have been calculated as the mean of the two separate values determined from the carbon dioxide in blood and expired air, and from the oxygen respectively. The chief reason for this has been that the use of two values provides a certain internal check on the validity of technique. Later work may show, as the comparisons just given suggest, that it will be more accurate to use

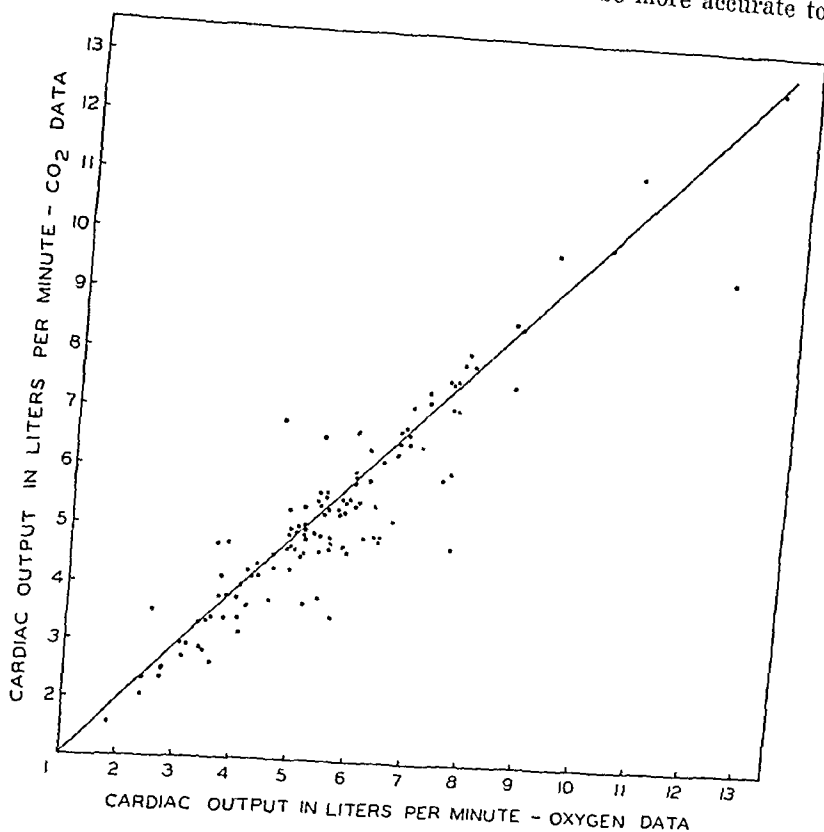


Fig. 1.—Scatter diagram showing the correlation between cardiac output calculated from  $\text{CO}_2$  data and cardiac output calculated from  $\text{O}_2$  data in 120 cardiac output determinations by the direct Fick method. The straight line is the line of identity. Although the mean of the values based on oxygen data is slightly higher than the mean of those based on  $\text{CO}_2$  data, this difference is not significant.

only the oxygen transport figures. No significant differences should occur, however, in groups of data, on this account. In Fig. 1 are plotted cardiac output figures in 118 determinations, including 59 determinations made on the patients reported in the present paper, ordinates indicating the value by  $\text{CO}_2$ , and abscissas by  $\text{O}_2$  calculation. There is a good correlation. The mean cardiac output by  $\text{CO}_2$  is 5.24 liters per minute; 5.51 liters per minute by  $\text{O}_2$ . The difference of means equals 0.27; standard error of difference of means equals 0.23. This difference between  $\text{O}_2$  cardiac output and  $\text{CO}_2$  cardiac output is statistically not significant. Cardiac output figures calculated sepa-



rately from the  $\text{CO}_2$  and the  $\text{O}_2$  data, in patients in shock, provide a better correlation than in normal subjects.

Control values of cardiac output and related measurements in fifteen normal subjects, studied under similar conditions, appear in Tables III and IV. The average values for cardiac index, stroke volume, and arteriovenous oxygen difference were respectively 3.42 liters per minute per square meter of body surface, 83 c.c. per beat, and 45 c.c. per liter of blood. The values for cardiac output and stroke volume are higher and figures for arteriovenous oxygen difference are lower, than corresponding figures reported on the basis of foreign gas methods. It will be noted that the  $\text{O}_2$  consumption per square meter of body surface in this series of fifteen normal individuals was somewhat high, indicating that some subjects at least were not in basal metabolic condition at the time of study. There are, however, reasons to believe that accepted figures for cardiac output as given by foreign gas methods are too low; a more complete discussion of this question will be published elsewhere.

*Cardiac Output by the Use of the Ballistocardiogram.*—During the early part of the investigation, ballistocardiographic tracings were taken as nearly as possible to the time of the cardiac output determination by the direct Fick method. The procedure followed was comparable to that previously described in normal individuals.<sup>9</sup> It soon became evident that in many instances the ballistocardiographic tracings were greatly influenced by the increased respiratory effort that was encountered. In Table II the results of twelve double determinations in nine subjects are listed, in which this disturbing factor was minimal. It can be seen that a reasonable agreement existed in subjects not in shock and with relatively large cardiac outputs. The cardiac output by the direct Fick method tended to be somewhat larger than the cardiac output calculated from the ballistocardiogram, even after the correction for cross section of the aorta had been introduced.<sup>9</sup> On the other hand, in patients suffering from shock, with one exception (Y. T.), differences were very significant and all in the other direction; that is, the data calculated from the ballistocardiogram were consistently larger. The data on two subjects, J. E. and E. C., repeatedly studied while in a state of shock following severe gastric hemorrhage, and again after recovery, emphasize strikingly the fair agreement in the latter state, and the large discrepancy in the former. Apparently some fundamental change occurs in the state of shock which invalidates assumptions upon which Starr's formulas were based. The two following suggestions are made: that as a result of marked decrease in blood volume, the capacity of the aorta and thereby its cross section is reduced; that the ejection velocity is increased as compared to that in normal conditions, an assumption supported by the change in contour (sharp initial peak) for the pressure curves in conditions with di-

TABLE III  
HEMODYNAMICS AND BLOOD VOLUMES

TYPE OF INJURY	NO. CASES	PULSE RATE	ARTERIAL PRESSURE			VENOUS PRESSURE (MM. H <sub>2</sub> O)	AURICULAR PRESSURE (MM. H <sub>2</sub> O)	CARDIAC OUTPUT			O <sub>2</sub> A-V DIFFERENCE (C.C. PER L. BLOOD)	PERIPHERAL RESISTANCE (DYNES CM. <sup>-5</sup> SEC.)	BLOOD VOLUMES		HEMATOCRIT (% R.B.C.)	SERUM PROTEINS (GM. %)
			SYST. (MM. HG.)	DIAST. (MM. HG.)	MEAN (MM. HG.)			CARDIAC INDEX (L. PER MIN. PER SQ. M.)	STROKE VOLUME (C.C. PER BEAT)	PLASMA (C.C. PER SQ. M.)			WHOLE BLOOD (C.C. PER SQ. M.)			
Normal Cases	13															
High		96	149	83	106	--	--	4.25	109	60	1755	--	--	--	--	--
Low		51	122	68	88	--	--	2.12	63	35	1100	--	--	2670	40	--
Average		74	137	74	97	74	33	3.42	83	45	1290	1600	2900	45	7.00	
Skeletal Trauma	8															
No shock																
High		58	167	87	113	92	70	4.32	100	50	1635	2070	3300	48	7.05	
Low		70	102	44	67	79	12	2.24	52	40	952	1130	1910	35	5.66	
Average		50	137	69	94	86	45	3.57	78	46	1281	1597	2791	41	6.35	
Mild shock	4															
High		140	113	50	67	105	47	2.71	39	82	1452	1675	2500	43	5.49	
Low		100	48	28	36	62	10	2.18	33	58	738	1376	1900	25	4.76	
Average		120	77	40	54	77	26	2.46	36	71	1019	1532	2330	34	5.22	
Moderately severe shock	4															
High		205	80	42	57	121	0	3.01	35	100	1468	1310	1820	37	5.91	
Low		112	46	15	22	50	-11	1.30	21	60	567	1033	1540	28	5.17	
Average		137	63	32	44	90	-8	2.06	26	84	1021	1125	1670	32	5.54	

Hemorrhage	1														
	High	131	135	95	105	18	24	2.09	44	84	2200	1780	2120	40	6.68
	Low	96	49	24	32	29	-31	1.38	17	57	828	850	1410	18	4.45
	Average	113	91	54	64	41	-1	2.20	31	70	1542	1325	1908	32	5.63
Burns*	1														
	High	112	136	71	100	--	42	2.30	78	106	3186	1230	2750	58	6.54
	Low	58	53	28	38	--	14	1.05	14	51	678	960	2120	42	6.23
	Average	91	--	--	--	--	--	1.814	39	--	--	1100	2320	51	6.44
Abdominal Injuries	3														
	No shock														
	High	128	182	91	132	85	31	4.18	85	64	2223	1700	3470	52	6.19
	Low	80	103	51	70	45	25	2.92	53	35	757	1075	2110	49	4.97
Shock	3														
	High	99	110	72	91	61	27	3.77	66	50	1260	1490	2993	50	5.74
	Low	156	112	48	69	39	3	3.21	38	97	1420	1360	2600	51	7.01
	Average	76	40	20	28	--	-30	1.24	22	73	610	--	--	44	5.60
Head Injuries	6														
	High	101	156	100	135	99	44	4.16	86	96	1710	1790	3070	45	7.29
	Low	57	131	74	96	35	-36	2.62	72	29	1122	1210	2590	39	5.75
	Average	79	157	85	111	65	6	3.66	79	62	1476	1563	2865	43	6.85

\* In two cases, measurements were incomplete, average was calculated only if measurements were complete in all four cases  
 † In one case, cardiac output figures from ballistocardiogram.

TABLE IV  
VENTILATION, RESPIRATORY GAS EXCHANGE, AND RESPIRATORY GASES IN BLOOD

TYPE OF INJURY	NO. CASES	RESPIRATION RATE	GAS EXCHANGE			ARTERIAL BLOOD							MIXED VENOUS BLOOD		
			VENTILATION (L. PER MIN. PER SQ. M.)	O <sub>2</sub> INTAKE (C.C. PER MIN. PER SQ. M.)	RESP. QUOT.	CO <sub>2</sub> (VOL. %)	PCO <sub>2</sub> (MM. HG)	T <sub>50</sub> (VOL. % CO <sub>2</sub> AT 40 MM.)	PH <sub>s</sub>	O <sub>2</sub> CONT. (VOL. %)	O <sub>2</sub> SAT. (%)	HB. (GM. %)	PCO <sub>2</sub> (MM. HG)	PH <sub>s</sub>	O <sub>2</sub> SAT. (%)
Normal Controls	15														
High		30	6.62	186	1.02										
Low		12	2.95	118	.61										
Average		18	5.07	154	.84	49.1	38.8	49.5	7.42	16.6	96.0	13.0	44.7	7.39	67.7
Skeletal Trauma	8														
No shock															
High		22	6.28	213	.86	50.6	42.8	49.0	7.43	18.5	97.4	14.2	48.2	7.39	76.3
Low		17	4.36	151	.66	42.7	30.4	41.8	7.36	13.1	91.0	10.7	38.3	7.33	58.0
Average		18	5.21	184	.74	44.1	37.4	45.0	7.39	15.6	94.2	12.3	43.9	7.36	66.7
Mild shock	4														
High		34	9.62	189	.80	40.1	33.4	44.0	7.41	14.4	95.0	12.5	39.5	7.35	42.9
Low		22	5.77	160	.65	32.7	27.0	37.0	7.32	9.8	85.7	8.0	32.0	7.29	35.0
Average			7.73	174	.70	35.8	30.5	40.2	7.38	12.3	90.8	10.1	36.9	7.32	38.4
Moderately severe shock	4														
High		36	18.46	285	.99	39.4	39.4	39.8	7.29	14.6	99.0	11.0	46.7	7.26	49.6
Low		17	4.35	131	.83	16.5	17.4	25.5	7.26	10.2	83.0	8.0	31.4	7.19	14.0
Average		29	11.19	176	.89	28.0	28.4	32.7	7.28	11.8	94.6	9.3	40.9	7.22	28.2

Hemorrhage	4	24	9.95	223	.75	57.2	53.6	53.4	7.37	14.6	97.1	11.6	66.0	7.33	48.0
		16	4.53	119	.70	30.3	25.7	36.4	7.30	6.6	95.2	5.1	32.2	7.28	16.2
		Average	21	6.35	154	.73	38.2	34.6	40.9	7.34	11.5	95.9	9.1	42.6	36.4
Burns*	4	22	4.10	126	.82	40.2	41.9	45.4	7.46	19.4	95.1	15.3	47.2	7.43	68.6
		8	2.41	109	.68	36.7	30.8	39.3	7.29	15.7	87.0	12.3	35.8	7.23	42.3
		Average	14	3.15	117	.74		41.8		18.0		14.5			
Abdominal Injuries	3														
		No shock													
		High	32	9.41	193	.75	50.8	46.5	48.0	7.42	20.0	95.7	15.6	37.5	74.0
Shock	3	Low	21	5.81	154	.72	28.6	27.7	33.9	7.32	17.2	93.0	13.8	32.0	62.0
		Average	27	7.43	178	.73	37.8	34.2	40.7	7.38	18.4	94.5	14.6		69.0
Head Injuries	6	High	45	12.30	236	.87	33.0	41.7	39.6	7.43	21.2	94.8	17.2	51.8	60.2
		Low	40	9.26	129	.73	29.0	26.3	28.4	7.17	12.0	72.8	12.3	32.7	15.2
		Average	42	10.63	189	.78	31.2	33.6	34.4	7.31	17.1	86.5	14.6	43.0	40.0
Average	6	High	38	14.32	353	.84	47.7	40.7	48.0	7.55	26.8	96.2	22.5	46.4	79.2
		Low	12	4.99	155	.69	37.7	24.8	44.9	7.38	15.4	88.8	11.9	29.2	34.3
		Average	23	10.00	247	.75	42.3	32.5	46.1	7.46	18.1	91.5	14.6	38.3	62.6

\*See note Table III.

minished filling of the arterial system (Wiggers). In either case the ballistocardiograph as calculated would give too high values.

As a result of these studies, we were led to discard the ballistocardiogram for the study of variations of circulation in patients in or recovering from shock.

*Peripheral Resistance.*—The total peripheral vascular resistance,  $R$ , was calculated from the formula:

$$R = \frac{P_m \text{ (mean pressure in mm. Hg)} \times 1332}{C.O. \text{ (cardiac output in c.c. per sec.)}}$$

The total peripheral vascular resistance, expressed in  $\frac{\text{dynes sec.}}{\text{cm}^5}$  repre-

sents the total fall of pressure from the root of the aorta to the right auricle per unit of total blood flow per second.<sup>12</sup> Mean pressure in the femoral artery is assumed to be equal to mean pressure in the aorta, and since auricular pressure, expressed in mm. Hg, is virtually zero, it is neglected.

The total peripheral resistance is an overall measurement of resistance to flow and, as such, does not permit differentiation of local vascular changes and compensations. Local variations in resistance to flow are mostly contributed to by cross-sectional changes in vessels; however, changes in viscosity, especially at low pressure, are not a negligible factor.

As for interpretation, it can be tentatively stated that: (1) A calculated resistance within normal range does not exclude vasoconstriction in some areas if compensated by decreased resistance to flow in other areas. (2) A calculated resistance greater than normal may indicate (a) a predominance of vasoconstriction in some areas over vasodilatation or normal vascular tone in other areas; (b) an increase in viscosity; (c) a combination of both. (3) A calculated resistance lower than normal may result from (a) predominance of vasodilatation in some areas over vasoconstriction in others; (b) a decrease in viscosity; (c) a combination of both.

*Respiratory Gases in Blood.*—The following information was obtained for both mixed venous and arterial blood:

CO <sub>2</sub> content of blood, vol. %	(CO <sub>2</sub> ) <sup>b</sup>
CO <sub>2</sub> content of serum, vol. %	(CO <sub>2</sub> ) <sup>a</sup>
CO <sub>2</sub> tension, mm. Hg	pCO <sub>2</sub>
CO <sub>2</sub> content at 40 mm. tension (alkali reserve), vol. % T <sub>10</sub>	
Hydrogen-ion concentration at 37° C.	pHs
O <sub>2</sub> content, vol. %	
O <sub>2</sub> capacity, vol. %	HbO <sub>2</sub>
O <sub>2</sub> saturation, %	%

CO<sub>2</sub> content, O<sub>2</sub> content, and O<sub>2</sub> capacity were determined directly and O<sub>2</sub> saturation calculated. In 68 per cent of the cases, hydrogen-ion

concentration was determined by the glass electrode method. A modified form of the MacInnes and Belcher glass electrode was used. The design permitted its being filled with mercury so that blood could be transferred from a pipette without contact with air. Samples were analyzed within fifteen minutes of the time they were drawn. Frequent control determinations with buffer solutions of known pH were made between sample determinations.  $(\text{CO}_2)^s$  and  $\text{pCO}_2$  were calculated, using the line charts of Van Slyke and Sendroy. The  $\text{CO}_2$  content at 40 mm.  $\text{CO}_2$  tension was estimated by making use of the alignment chart of Henderson, Bock, Dill, and Edwards.<sup>13</sup>

In 32 per cent of the cases one or two points on the  $\text{CO}_2$  dissociation curve were determined by the tonometer technique. Use was made of the Henderson, Bock, Dill, and Edwards chart in the calculation of  $\text{pCO}_2$  and  $\text{T}_{40}$  and of the Van Slyke and Sendroy line charts in the determination of  $(\text{CO}_2)^s$  and hydrogen-ion concentration. Normal control values appear in Table IV.

*Lactic Acid.*—Lactic acid was determined by oxidation with ceric sulfate according to the microdiffusion method described by Winnick.<sup>14</sup> A misleading statement made by Gordon and Quastel<sup>15</sup> concerning the absence of oxidation of ethyl alcohol by ceric sulfate, invalidated at first all determinations made in subjects studied in a state of alcoholism. More recently, a modification of the original method has been developed, making possible the accurate determination of lactic acid in the presence of alcohol. Other controlled experiments have indicated that the presence of mannitol, a substance used for the measure of plasma flow through the kidney, has no effect upon lactic acid determinations.

*Renal Clearances.*—The renal clearance of mannitol has been used as a measure of the glomerular filtration rate<sup>16</sup> and the clearance of p-aminohippurate as a measure of the renal plasma flow.<sup>17</sup> Priming doses of 18 Gm. of mannitol,\* and of 16.8 mg. per pound of body weight of p-aminohippurate were given intravenously, followed by intravenous infusion of 5 per cent mannitol and 200 to 300 mg. per cent p-aminohippurate solution at a rate of 4 c.c. per minute. After a 15-minute discard period, urine was collected by indwelling catheter and arterial blood taken at intervals. Mannitol in cadmium filtrates of plasma and in diluted urine<sup>18</sup> was determined by the modification of the method of Silberstein, Rappaport, and Reifer,<sup>19</sup> described by Smith, Finkelstein, and Smith.<sup>16</sup> Sodium p-aminohippurate was determined in the same cadmium filtrates and urines by a colorimetric method.<sup>20</sup>

In addition to (a) glomerular filtration and (b) plasma flow expressed in cubic centimeters per minute, the following data were calculated: (c) Filtration fraction, the proportion of the plasma flowing through the kidney, which is filtered at the glomeruli; (d) effective

\*The mannitol and p-aminohippurate, etc., used in this study were supplied by Sharp and Dohme.

renal blood flow, calculated from plasma flow and hematocrit by the formula

$$\text{R.B.F.} = \frac{\text{clearance of p-aminohippurate}}{100 - \text{hematocrit } \%} \times 100$$

(e) Renal fraction, the percentage of the total cardiac output which passes through the kidneys, expressed as

$$\text{R.F.} = \frac{\text{R.B.F., lit./min.}}{\text{C.O., lit./min.}} \times 100$$

The figure for cardiac output was taken either from the observation nearest to the time of renal study, if the patient's condition had not changed, or as an average of two cardiac output determinations, one before, the other after renal clearance studies, when the condition had changed. (f) Average urine flow in cubic centimeters per minute. This volume, as measured, has been influenced by the injection of hypertonic solution of mannitol, and thus is presumably greater than the true urine flow obtaining in the given state of the circulation at the time.

It is assumed that mannitol filtration is not altered during shock, and that the clearance of this substance is a measure of the glomerular filtration rate. In the case of sodium p-aminohippurate, however, it may very well be argued that anoxia in the course of shock causes decreased activity of the mechanism by which it is excreted into the tubules and thereby results in the failure of complete extraction. This would lead to falsely low values for the rate of renal plasma flow, and thus to falsely high values for filtration fraction. In the course of this investigation, the filtration fraction in the majority of instances so far studied has been either normal or quite low, in the presence of marked anoxia, and apparently a reduced effective renal flow.

#### MATERIAL FOR STUDY

The material upon which the present paper is based includes 36 cases, of which the patients in 16 were suffering from skeletal trauma, 4 from hemorrhage, 4 from burns, 6 from abdominal injury, and 6 from head injury.

Patients in the 16 cases of skeletal trauma all suffered from multiple, usually compound or comminuted, fractures of the limbs. Three among them had special features: one had fractured ribs with hemopneumothorax and paradoxical motion of the chest wall; another had, in addition to a fracture of the pelvis, a fractured skull and slightly bloody spinal fluid; a third developed a very severe infusion reaction during the course of the study. The patients in 8 out of these 16 cases were considered to be suffering from shock, when first observed. Repeat measurements were made after spontaneous clinical improvement or after institution of treatment of the shock condition.



The 4 cases of hemorrhage consisted of 2 subjects with massive hematemesis due to ulcer, one with intestinal bleeding due to a ruptured vein in the small intestine, and one with external bleeding from self-inflicted cuts of the neck and arms. All 4 patients were considered to be in shock of varying intensity at some time during the period of observation. One of these was found upon recovery to present evidence of arterial hypertension.

Four patients with burns were studied; in 2 of them approximately one-third of the body surface was involved; in 1, about one-quarter; and in the fourth, the face and both hands. Depth of burns ranged from first to third degree.

Three patients with abdominal injuries, suffering respectively from a ruptured peptic ulcer, a ruptured urinary bladder, and necrosis of the sigmoid and rectum following an enema with a caustic substance, were not considered to be in shock at the time of study. One of these cases, on recovery, was found to have arterial hypertension. The 3 other patients with abdominal injuries presenting clinical manifestations of shock, suffered from incarcerated hernia, ruptured ileum, and intestinal obstruction respectively. The patient with intestinal obstruction was in a moribund condition when studied.

The 6 cases of head injury were all comatose, and prognosis when first seen was considered to be fatal. At autopsy in addition to subdural and/or subarachnoid hemorrhage, multiple punctate hemorrhages of the pons and other parts of the brain stem were found. They were all first studied during the period of arterial hypertension and progressive hyperthermia, and then followed until death.

Sixteen, or 45 per cent of the total number of 36 patients died, and 11 were autopsied.

#### CLASSIFICATION AND CLINICAL MANIFESTATIONS

Primary subdivision of all clinical material on the basis of type of injury, as already indicated above, has been retained in the presentation of physiologic data, since the actual results were found to group themselves most satisfactorily in this manner.

A secondary differentiation as to the degree of shock has also been made. This has been done in the light of all available data, including the extent and time of injury, clinical manifestations on admission, the laboratory findings, and the subsequent clinical course.

*Skeletal Trauma.*—Of the 16 cases in this group, 8 were classified as having “no shock,” 4 “mild shock,” and 4 “severe shock.”

In spite of the absence of specific clinical criteria by which to evaluate the severity of shock, the overall clinical impressions at the time of study of these 16 patients with skeletal trauma were fairly consistent with the classification made in retrospect. Thus, clinically, none of the patients in the “no shock” group were considered to be in shock

at the time of study, although, in most cases, shock had been anticipated because of the severity of the injuries. Of the 4 patients in the "mild shock" group, 1 showed no clinical evidence of shock and 2 appeared to be in moderately severe shock. One of the latter cases was complicated by chest injury, with paradoxical motion of the chest wall, and the other by acute alcoholism, both conditions having brought on shock-like symptoms which were difficult to evaluate. All 4 cases in the "severe shock" group were so described on clinical grounds.

More exact evaluation of the individual patient, on the basis of clinical manifestations, was most difficult, both because the signs and symptoms were so varied from one patient to another, and because such manifold changes frequently were seen in the same patient within a relatively brief period of time. A few general descriptive comments can be made.

Patients not in shock had more symptoms and fewer signs, those with severe shock fewer symptoms and more signs. Pain, for example, was present in all "no shock" cases, but absent in one-half of the cases with "mild" or "severe" shock. Apprehensiveness was less often seen in patients in severe shock in this group. These patients, in fact, were usually apathetic, quiet, cooperative, rational when roused, without physical complaint, and without anxiety. Not infrequently as a patient emerged from shock he began to be restless and complain of pain. They were usually much more disturbed about the various examinations made, after recovery, than they had been on admission, during shock.

Of individual symptoms, thirst was the most constant. Pallor and coolness of extremities paralleled in a general way the severity of shock; but the subjective sensation of cold might be complained of whether the patient was in shock or not. This sensation was often associated with some shivering. Transient nausea and vomiting occurred at some time in almost every case of shock. Sweating was frequent but usually a fleeting phenomenon. The arterial pulse in shock was thready, often imperceptible at the wrist; the rate was quite variable. The peripheral veins were usually small and collapsed; a needle could usually be introduced readily, though often blood could not be withdrawn. Cyanosis and mottling of the skin, usually a terminal finding, were occasionally seen in patients whose condition was not serious.

*Hemorrhage.*—The group of 4 hemorrhage cases was too small to subdivide. It is, therefore, not homogeneous either with respect to the type of bleeding or to the depth of shock. Some of the clinical manifestations, including thirst, mental and emotional depression, and thready pulse, corresponded closely to those of the skeletal trauma group. Pallor, coolness of the extremities, and collapsed veins were more prominent, while pain and sweating were less in evidence. The tendency to vomit could not be compared because of hematemesis in two of the cases.

Restlessness was observed in association with active bleeding at a time when the patient had already lost large quantities of blood.

*Burns.*—The patients in 3 out of 4 cases were considered to be in shock when first examined. In contrast to the previous group in shock, restlessness and pain were prominent; thirst and vomiting were also present.

*Abdominal Injuries.*—The differentiation of the cases of abdominal injury into those with and those without shock present was clear-cut, upon review of all the data. The 3 patients without shock were in good condition; all were operated upon successfully and recovered. The 3 others were in advanced shock: 1 died within an hour after the study was completed, the other 2 both died within twenty-four hours of the time of study.

In general, the patients with abdominal pathology showed more of the usual clinical signs and symptoms of shock than those with skeletal trauma or hemorrhage with a comparable degree of circulatory failure.

*Head Injuries.*—The head injury cases contrasted sharply with the other groups. Studied initially in the phase of hypertension and hyperthermia, they had bounding pulses and burning hot skin over the head and trunk. The extremities remained cool and dry. The respirations were both deep and rapid and frequently became stertorous due to falling back of the tongue or to partial obstruction of the airway by aspirated material. All patients in this group were comatose, had no cough reflexes, and vomited, making aspiration of vomitus into the lungs almost inevitable unless the stomach was kept empty by means of a Levine tube. A metal pharyngeal airway and frequent use of suction helped to maintain a free air passage. These patients showed none of the clinical manifestations of shock.

## RESULTS

### *State of the Circulation in Various Types of Injury*

In Tables III and IV and Fig. 2 are given, for each type of injury, the means and the range of variation of the following measurements:

(a) Blood volume and its components, (b) arterial blood pressure, (c) right auricular and peripheral (arm) venous pressures, (d) cardiac output and the state of respiratory gases in arterial and mixed venous blood, and (e) respiratory gas exchange.

Inasmuch as the comparison sought for in the tabulation was the *state of shock* versus the *state of nonshock*, that particular series of measurements was chosen, on each patient in shock, which showed the greatest deviations from normal, i.e., the severest shock picture. The table contrasts the group picture, so to speak, of the circulation in shock, constructed in this way, against the group picture of the circulation of injured subjects not in shock. The progressive change, as a given patient moves from shock to recovery, is considered in a subsequent section.

For purposes of reference, at the top of the tables are given a set of normal values of the various functions measured.

*Skeletal Trauma Without Manifestation of Shock.*—The findings in this group may be compared to average values obtained in normal sub-

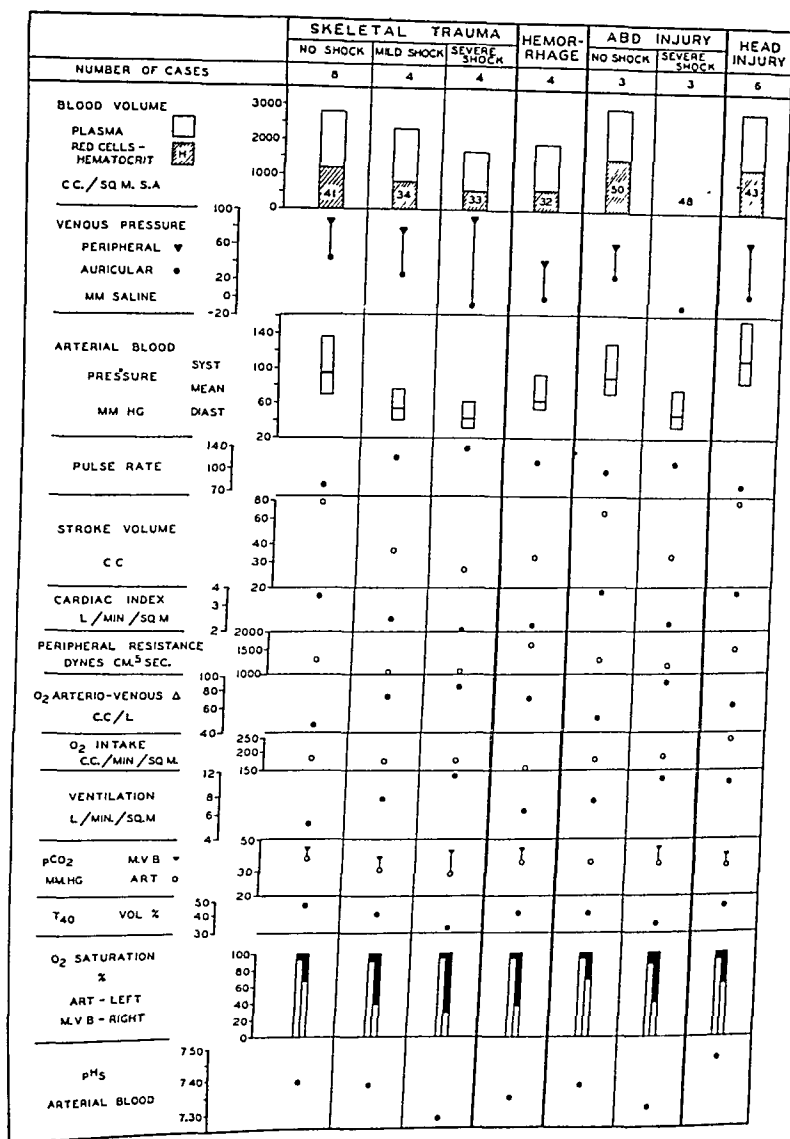


Fig. 2.—Graphic representation of average measurements shown in Tables III and IV. (For mode of grouping and description of measurements see text.)

Blood volume, venous and auricular pressures, arterial blood pressure, pH and O<sub>2</sub> saturation of arterial blood, measurements plotted against the solid block represents the oxygen content, the open block the oxyhemoglobin per cent of total hemoglobin.

For approximate normal control values, see Tables III and IV. No values are plotted for blood volume and peripheral venous pressure in the abdominal injury group with severe shock, since the data for this group were incomplete.

jects. The metabolic conditions under which the two groups were studied, while not strictly basal in either group, were comparable.

It can be seen that the hemodynamic status of cases with severe trauma without clinical manifestations of shock, is close to normal. Differences in pulse rate, arterial, venous, and auricular pressures, blood volume, cardiac output, peripheral resistance, ventilation, oxygen consumption, and the oxygen saturation, carbon dioxide pressure, alkali reserve, and hydrogen-ion concentration of both arterial and mixed venous blood, are well within the range of normal variation. Hematocrit and plasma protein were slightly below normal figures. Thus, the injured individuals who showed no clinical or other manifestations of shock were found to have a circulatory status within normal limits except for slightly low hematocrit and plasma protein.

*Skeletal Trauma With Mild and Severe Shock.*—The picture of peripheral circulatory failure in these cases was definite and consistent, as shown in the tables and figure. The chief findings in severe shock may be grouped as follows:

*Blood volume:* Blood volume was sharply decreased, the average value being little more than one-half normal. Red cells were decreased more than plasma, as indicated by low hematocrit reading. In no instance, in this group, was there any evidence of hemoconcentration.

*Intravascular pressures:* Arterial blood pressure was low, average mean pressure being just under 40 mm. There was a tendency for systolic pressure to fall more than diastolic, pulse pressure thus being also diminished.

Pressures in the right auricle, expressed in relation to atmospheric pressure, were consistently below normal. Every patient in severe shock had an auricular pressure of 0 or below. Pleural pressures not having been measured, the effective pressure of venous return to the right auricle was not determined.

Peripheral (arm) venous pressures, on the other hand, were not decreased, sometimes even elevated above normal in severe shock.

*Cardiac output:* This fundamental function was decreased, the mean value in severe shock being less than two-thirds normal. There was one exception (Table I), patient A. A., who was having a severe shaking chill at the time of study, with a temperature of 103° F., rising shortly after to 107° F.

*Respiratory gas exchange:* Pulmonary ventilation was increased in severe shock, though not in every case; it was probably associated with uncompensated acidosis. Oxygen consumption, on the other hand, was slightly subnormal. The single exception here was, again, the patient with the shaking chill and high temperature. Arterial blood was normally saturated with oxygen, except in a few instances with known pulmonary disease. Mixed venous oxygen was therefore decreased ap-

proximately in proportion to the decrease in cardiac output. This is well shown in the chart.

*Acid-base equilibrium:* Alkali reserve and arterial hydrogen-ion concentration were both sharply decreased, an uncompensated acidosis. In some instances the acidosis was very marked. High blood lactic acid figures indicated that fixed organic acids played a large part in producing this change. Mixed venous hydrogen-ion concentration fell even more than arterial in shock, the arteriovenous differences in hydrogen-ion concentration being thus increased.

It was at first thought that an acidosis of this kind was an essential feature of the shock picture in skeletal trauma. In more recent studies (subsequent to the series here reported) we have found that in early shock (within the first two or three hours), pH is still normal, even though the degree of shock may be severe; uncompensated acidosis develops in succeeding hours.

Perhaps the most striking feature of the results in the group of cases in mild shock is that they are in every respect consistent with the findings in severe shock. In other words, in every significant measurement the value in mild shock lies between the two extremes, on the one hand the normal figure, on the other that in severe shock.

*Hemorrhage.*—The blood loss in the 4 cases comprising this group could not be quantitatively estimated with any degree of accuracy. Blood volume studies, however, indicate not only different amounts of bleeding but also differences in the extent of hemodilution. On an average, blood volume was about two-thirds of normal and midway between values observed in the mild and in the severe shock groups with skeletal trauma. Average values of auricular pressure, cardiac output, stroke volume, mixed venous oxygen and arterial hydrogen-ion concentration also fell between similar values in the two latter groups. However, there were some differences worth noticing between the group with hemorrhage and the groups with severe trauma in shock: (1) The proportionally higher value of arterial blood pressure and peripheral resistance in the hemorrhage group, (2) the lower oxygen consumption, (3) the lower ventilation resulting in somewhat higher  $p\text{CO}_2$  values in both arterial and mixed venous blood, (4) the lesser pulse rate increase. It must be noted that average values of arterial blood pressure and peripheral resistance are somewhat distorted by the values observed in one subject (E.C.) who later was proved to be suffering from arterial hypertension; nevertheless, one patient (C.F.) to be discussed in the second paper in greater detail, with the lowest blood volume and cardiac output of the group, still maintained a relatively high arterial blood pressure, and had therefore by calculation an abnormally high peripheral resistance.

In summary, apart from the differences noted above, which may be chance variations and which require further investigation, the status

of circulatory dynamics in patients with hemorrhage is closely similar to that in patients in shock due to severe trauma.

*Burns.*—This group is not very homogeneous with regard to extent of burns, or the time intervals between injury and study. The initial measurements were, however, taken before treatment with plasma had been started. In addition, because of technical difficulties due to the distribution of burns, some of the measurements are missing. Description of individual cases, (to be reported later), followed over a long period of time, will give a more complete picture especially with regard to the relation of plasma loss to hemodynamic change. Certain definite trends, however, can be noted (Tables III and IV): (1) The large decrease in plasma volume with high hematocrit and relatively normal plasma protein; (2) the consistently low figures for cardiac index and stroke volume; (3) the lesser increase in pulse rate than in other groups; in one patient with severe shock, and very low blood pressure, the pulse rate was 58; (4) the low ventilation and low oxygen consumption; (5) the rather small decrease in alkali reserve.

*Abdominal Injury Followed by Prompt Recovery.*—This group of 3 patients was not in shock and the state of their circulation was normal. A further proof of their condition was that all three underwent major operative procedures shortly after study, and made uneventful recoveries.

With minor variations, values for blood volume, auricular and peripheral venous pressure, cardiac output, stroke volume, and arteriovenous difference were well within the normal range. Due to findings in one patient, who later proved to be hypertensive, the average arterial blood pressure was slightly above normal; the range of values of peripheral resistance on this account is quite large. Consistent with the normal state of circulation were the normal state of respiratory gases, alkali reserve, and level of hydrogen-ion concentration in both arterial and mixed venous blood. As expected with infradiaphragmatic pathology, resulting in distended and rigid abdominal wall, there was some hyperventilation. The single striking difference between this group and that represented by normal controls and by patients with skeletal trauma not in shock, was the high hematocrit. Infection, fever, vomiting, and the relatively long duration of some of these abdominal conditions may have been factors responsible here.

*Abdominal Injury Followed by Death.*—In this group of 3 patients, all in profound shock, death occurred within a short period of time following observation. In only 1 case was blood volume measured; this was only slightly below normal figures. Average figures of arterial blood and auricular pressure, of cardiac output and stroke volume were all low; in 1 patient, who died within one hour, the lowest figure of cardiac output of the series was recorded. Hyperventilation was marked, arterial hydrogen-ion concentration low, and the arteriovenous

difference in  $pCO_2$  was large. Again in this group, hemoconcentration was present to the extent that hematocrit was high, although plasma protein concentration was normal.

*Fatal Head Injury During Period of Arterial Hypertension.*—The group of 6 cases with extensive brain damage was first studied during the period of arterial hypertension, which preceded death by variable but always brief intervals of time. The state of the circulation was then in sharp contrast with that observed in patients with severe skeletal trauma and shock, hemorrhage, burns, and fatal abdominal injury. With a blood volume on the low side of normal, the cardiac output was either normal or somewhat elevated. Wide variations in auricular pressure, resulting from very abnormal depth and quality of respiration, either gasping and stertorous as in most instances, or groaning, rendered any reading difficult to record and interpret. The peripheral resistance was on the upper side of normal. Apart from a tendency to gaseous alkalosis resulting from hyperventilation, all findings in arterial and mixed venous blood were normal.

*Changes in Circulation Occurring During Recovery From Shock*

Data in 6 subjects, 4 with skeletal trauma and 2 with hemorrhage, who were studied in the state of shock and again shortly after recovery from shock, following blood transfusion, are tabulated in Table V.

TABLE V

COMPARISON OF AVERAGE MEASUREMENTS IN STATE OF SHOCK AND AFTER RECOVERY FROM SHOCK, FOLLOWING BLOOD TRANSFUSION, IN SIX SUBJECTS\*

MEASUREMENTS	SHOCK	RECOVERY
Body temperature ( $^{\circ}C$ )	37.8	37.3
Pulse rate	115	103
Arterial blood pressure (mm. Hg)	69/35	120/62
Auricular pressure (mm. $H_2O$ )†	+5	+23
Cardiac index (liters per $m^2$ b.s.)	1.96	2.99
Stroke volume (c.c. per beat)	28.3	39.0
Oxygen art.-ven. difference (c.c. per liter blood)	81	55
Plasma volume (c.c. per $m^2$ b.s.)‡	1362	1629
Total blood volume (c.c. per $m^2$ b.s.)‡	1665	2503
Ventilation (liters per $m^2$ b.s.)	7.82	7.53
Oxygen intake (c.c. per $m^2$ b.s.)	156.5	182.5
Art. blood $CO_2$ cont. at 40 mm. Hg (vol. %)†	35.8	43.5
pH <sub>a</sub> (arterial blood)	7.31	7.37
Mixed venous blood $O_2$ sat. (%)	35.8	52.7

\*4 with skeletal trauma, 2 with large hemorrhage.

†Average of 5.

‡Average of 4.

The average amount of blood transfused was 1170 c.c. and in addition an average amount of 1780 c.c. of saline solution was injected. The time interval between the two sets of measurements was, on an average, five hours (excepting one case in which the second study was forty-eight hours after the first). Improvement in circulation was striking; arterial blood pressure returned to normal levels while blood volume and cardiac output increased both approximately by 50 per cent of their previous



values; auricular pressure increased by 20 mm.  $H_2O$ , the three latter measurements being still below normal values. Alkali reserve and hydrogen-ion concentration showed similar trends. Hyperventilation and high pulse rate usually persisted. Oxygen consumption increased somewhat.

In brief, these data show the manner in which the circulation in peripheral failure, as seen in hemorrhagic or traumatic shock, can be restored by blood transfusion.

### *State of Renal Circulation in Relation to Shock*

The material collected does not as yet permit an estimation of the effect of shock upon renal blood flow and rate of glomerular filtration. Data on one control group provided by head injuries, and isolated observations in other types of injuries with various states of the circulation, have been tabulated in Table VI. They should be viewed only as indicative of trends, to be supported by further investigation still in progress.

TABLE VI  
RENAL CIRCULATION IN VARIOUS TYPES OF INJURIES

TYPE OF INJURY	PATIENT	MEAN ARTERIAL BLOOD PRESSURE	CARDIAC OUTPUT (L. PER MIN.)	GLOMERULAR FILTRATION (C.C. PER MIN.)	EFFECTIVE RENAL PLASMA FLOW (C.C. PER MIN.)	FILTRATION FRACTION	TOTAL RENAL BLOOD FLOW (C.C. PER MIN.)	RENAL FRACTION (%)	URINE FLOW (C.C. PER MIN.)
Normal control		--	--	130.0	688.0	.189	--	20.0	--
Head injury	Average of 5 cases	86	5.7	113.4	552.3	.205	990	17.3	4.62
Skeletal trauma—	J. V.	40	2.3	too low to be measured					
profound shock	A. A.*	54	5.1	2.6	22.7	.115	32	0.6	0.10
Hemorrhage									
(a) profound shock	H. M.	45	3.1	5.1	108.0	.047	160	4.5	0.34
(b) during recovery from shock	C. F.	90	3.1	42.9	194.9	.220	310	10.0	2.95
Abdominal injury									
(a) no shock	L. P.	72	7.2	110.1	690.0	.165	1352	18.8	5.60
(b) profound shock	J. D.	73	3.9	2.0	11.3	.178	22.0	0.6	0.17

\*Very severe infusion reaction.

The average results in 5 cases of head injury, studied during periods of hypertension, show only slight deviation from normal findings, indicating that kidney circulation, like general circulation, remained essentially unaltered.

Results in 2 cases of severe shock due to skeletal trauma observed at their worst indicate extreme reduction in urine flow, too low to be measured accurately in J. V. In A. A., who suffered a severe infusion reaction with chills and fever throughout the renal study, the interpre-

tation is somewhat difficult; it is seen, however, that there was a very great decrease in filtration rate, effective plasma flow, or effective blood flow, and renal fraction.

In one hemorrhage patient in profound shock, the results are somewhat similar, with minor differences. In the second case of hemorrhage, given blood transfusion (blood bank) during the period of clearances, having a relatively high arterial mean pressure, the state of the renal circulation is somewhat better, especially the rate of filtration.

Of 2 cases of abdominal injury, one patient without shock showed normal renal circulatory dynamics. In the second case, a considerable reduction in effective renal blood flow was noted. This patient was in profound shock, in spite of the fact that the arterial blood pressure was not greatly decreased, the mean pressure being, as a matter of fact, the same as that of the first patient. A further interesting finding was a normal filtration fraction in this second (shock) case.

#### DISCUSSION

The descriptive data obtained in the present study indicate that *traumatic shock* is a rapid or precipitate failure of the circulation, usually associated with inadequate return flow of blood to the heart. This is in accord with the generally accepted view of shock, as developed in animal and in clinical studies.

If the above definition is valid, then the severity of shock should be consistently measured by the extent of decrease in cardiac output. Our results bear out this statement, the cardiac output being apparently a good index of shock in every case except two; one patient with fractured pelvis, who was having a violent shaking chill at the time of study, and one abdominal injury with fever and high oxygen consumption. The arteriovenous differences were, however, high in both these cases.

Equally consistent was the rise in cardiac output as the patient emerged from shock. This is shown in Table V. It will be better illustrated by individual case reports, in a subsequent paper.

The obvious question at this point is, how we have assigned the various patients into the categories of "shock" and "no shock," and whether we are not creating these categories simply on the basis of the measurements themselves. As stated in the body of the paper, the classification of each patient has been the best estimate that we have been able to make, using all available information—the clinical descriptions of the patient at the time, the sum of the measurements made, and especially the clinical course which the patient pursued. Using all these sources, there was actually but little if any doubt as to whether a given patient was in shock or not, at the time of initial study.

The anatomic factor immediately responsible for circulatory failure in our cases appeared in most instances to be a deficit in blood volume.

The average loss of blood volume, in cases in severe shock, was about 40 per cent. The equally important question whether a state of shock can develop without significant loss in circulating blood volume was not directly answered by the data presented in this paper. Further evidence on this problem, and its relation to so-called "primary" or "neurogenic" shock, will be offered in later papers.

Hemodilution, rather than hemoconcentration, was found in all cases of skeletal trauma with shock, and in all hemorrhage cases except one. While added plasma and saline solution might have been factors in this hemodilution, in the studies carried out during and after treatment, this could not apply to the initial measurements made usually soon after admission; and in these also, hemodilution was regularly demonstrated. In the skeletal trauma cases, the mechanism appeared to be chiefly extravascular blood loss (hemorrhage into tissues), followed by compensatory inflow of fluid from the tissues.

This finding (hemodilution) is of some importance in demonstrating that in these particular groups of cases of clinical shock, neither "increased capillary permeability" in the usually accepted sense, nor the consequent hemoconcentration, was present or played any part in the shock mechanism.

In burns and abdominal injuries, hemoconcentration was found.

If shock is due to failure of venous return, then the "effective pressure" of blood in the right auricle in states of shock should be consistently low. This we were not able to demonstrate precisely, since our auricular pressures were measured with reference to outside atmospheric pressure, rather than to intrathoracic pressure. This is an important point, since it is known that intrathoracic and intra-auricular pressures vary greatly with changes in form of respiration. Examples of this are, in fact, given in some of our patients with head injury, whose exaggerated stertorous breathing sucked the auricular pressures well below atmospheric levels, even though cardiac output was normal. It is also true that there is among normal subjects a considerable variation in the recorded right auricular pressures.

Admitting deviations due to irregular respiration and to individual differences, it is nonetheless probably significant, as shown in Tables III and IV, that the average figures for auricular pressure decreased progressively with increasing severity of shock, and (Table V) increased again as the patient recovered. Individual studies show instances of established shock in which auricular pressures were still within the lower limits of normal (+20 mm. of water); but we have had no case of shock with elevated auricular pressure, save for a patient with pulmonary embolus not included in this study. This is probably best considered as a special case, of acute failure of venous return to the left heart.

It can be stated, therefore, that our average figures on right auricular pressures suggest failure of venous return, in the patients in shock, and that none of the data are inconsistent with this hypothesis.

While the degree of shock was well correlated with the fall in arterial (femoral) blood pressure, this relationship was not constant in all instances. Two patients obviously in severe shock on admission had mean blood pressures within normal limits. Another had a rise of pressure to normal during the early part of treatment, without emerging from shock. These cases will be described in detail in the next paper of the series.

It is to be noted that the systolic pressure regularly fell more than the diastolic in shock, with, therefore, a reduced pulse pressure. During recovery, also, the systolic pressure increase was greater than that of the diastolic.

Low arterial pressure raises the question of inadequate coronary blood flow and of myocardial weakness. If this existed, it never extended to the point of congestive failure, since auricular pressures remained low. Thus, as already stated, the failure of venous return appeared to be the dominant factor.

Increase in pulse rate was variable and not a reliable criterion, or well correlated with the other data.

Adequate methods of determination of mean arterial pressure and of cardiac output have made possible the calculation of total peripheral vascular resistance. As will be seen from the figure and tables, the average values indicate that total peripheral resistance is not regularly increased in cases of shock. It should be emphasized, however, that the range of variation, from one individual case to another, was very large, extending from extremely low to moderately high values. Also, it was not infrequent to find low values for total peripheral resistance, when at the same time there was evidence of marked vasoconstriction in local vascular systems, specifically the skin of the extremities, and the kidneys. The cases of hemorrhage with shock showed, on the average, a somewhat higher peripheral resistance than the cases of skeletal trauma with shock, but this difference cannot be considered significant, with the present limited data.

That no consistent trend was observed may be due, among other causes, to great variations in the amount and rate of blood and fluid loss, changes in blood viscosity, and the degree of peripheral circulatory failure. Obviously, great differences existed in the pattern whereby the capacity of the vascular system as a whole adapted itself to loss in circulating blood volume. Detailed study of the adaptation in individual cases may give more useful information on this problem.

One local phase of vascular status receives some elucidation from the comparison of peripheral arm venous pressures with central auricular pressures. The tendency for this particular peripheral-central pressure

gradient to increase during shock gives support to the concept of narrowing of the venous channels in the extremities. It is not known whether this is on the basis of active venospasm or of passive collapse from lack of blood volume.

The considerable decrease in effective renal flow observed in the few subjects studied in a state of severe shock indicates either that the head pressure in the afferent artery is too low to promote filtration and effective flow and/or that active constriction is taking place. The latter mechanism would suggest that the kidneys, like the skin, are temporarily cut off from the circulation, thus making available more of the limited blood supply for immediately essential bodily functions. This adjustment of the renal circulation would play an important part in the attempt to maintain vascular hemostasis during periods of stress. The data on filtration fraction collected in patients in severe shock or during recovery from shock, suggest that the marked reduction in effective renal plasma flow is not primarily the result of failure of extraction of p-aminohippurate, but rather represents a true decrease in the circulation through the kidneys. These and other questions will be discussed in a separate paper dealing with the renal circulation in shock.

Total metabolism tended to be low in our cases of shock, acid-base levels decreased, with uncompensated acidosis. Blood lactic acid was much increased, accounting for a large part, if not all, of the fixed acid increase. Further data on this point will be presented in a subsequent paper. It might be noted that in two patients in profound shock, blood potassium was measured and found to be less than 6 mg. per 100 c.c. Uncompensated acidosis may not be present in the early hours following injury, even though the degree of shock is severe. Acidosis is, however, regularly present in later stages. It usually tends to disappear as recovery takes place, but in one patient (J. V.), the circulation recovered while acidosis actually became more marked.

It will have been apparent from this report that we conceive of shock as an end stage of circulatory failure which may be approached in many different ways. Each type of injury produces its own set of disabling factors, whose resultant and final effect is a form of failure of the circulation that we recognize as shock. In the limited clinical material reported in this study, the state of shock occurring in skeletal trauma was found to be closely similar to that in hemorrhage. Burn shock differed chiefly by the existence of massive loss of blood plasma; abdominal injuries also showed hemoconcentration.

Almost all of our patients in shock had considerable losses of blood volume and were of the "secondary" type. Vascular or vasomotor collapse (so-called primary or neurogenic factors) may well have been of essential importance also, in some cases; but it was not possible to identify these factors with certainty.

There are many important forms of injury that were not encountered in our material, as well as complicating factors such as exposure, dehydration, pre-existing emotional states of various kinds. Further cases which we have subsequently studied may partly fill in these gaps.

#### SUMMARY

1. Measurements of the circulation have been carried out in 36 clinical cases of injury of various types, with varying degrees of shock. The primary purpose has been a descriptive study of shock in man.

2. The basic measurements employed have included: (a) plasma and blood volumes; (b) arterial, and peripheral and central (right auricular) venous pressures; (c) cardiac output (direct Fick technique), (d) blood gases, hydrogen-ion concentration, lactic acid, proteins; (e) pulmonary ventilation and respiratory gas exchange; (f) renal clearances.

3. Critical evaluation of the methods used has been presented.

4. The clinical material consisted of 16 cases of severe skeletal trauma, 4 cases of hemorrhage, 4 cases of burn, 6 abdominal injuries, 6 cases of head injury.

5. The description derived from the data obtained conforms to the accepted view that traumatic shock in man is a rapid or precipitate failure of the circulation, usually associated with inadequate return flow of blood to the heart. The chief findings were decreased cardiac output, low pressure in right auricle, low arterial pressure, and decreased blood volume.

6. The cases of shock due to skeletal trauma and those due to hemorrhage, with one exception, all showed hemodilution rather than hemoconcentration. Burns and abdominal injuries showed hemoconcentration.

7. In 6 patients studied while in shock, or during recovery from shock, measurement of renal clearances showed marked reduction in effective renal blood flow, out of proportion to the decrease in the systemic blood flow, with a filtration fraction either normal or low.

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# Review of Recent Meetings

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## REVIEW OF FIFTH ANNUAL MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS

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THE Fifth Annual Meeting of the Society of University Surgeons was held in Chicago, Ill., at the University of Chicago Clinics, Feb. 11, 12, and 13, 1943. Papers presented are published in this issue of *SURGERY*.

In addition to those appearing here, Edward L. Howes, New York, discussed the rate and nature of epithelization of experimental wounds and described a photographic method for recording this phenomenon. Herbert C. Maier, New York, reviewed the physiologic disturbances caused by mediastinal displacement after pneumonectomy. Frederick E. Kredel, Charleston, S. C., presented further results and follow-up in a series of patients subjected to myopexy for amelioration of residual paralysis after cerebral thrombosis. D. Slaughter, Chicago, reviewed current conceptions of the indications for surgical and irradiation treatment of tumors of the skin. Repair of large bone defects by massive bone grafts was discussed by D. B. Phemister, Chicago. A series of patients with solitary fibrous lesions in the long bones was presented by C. H. Hatcher, Chicago. The various surgical procedures for relief of intractable pain were described by E. A. Walker, Chicago. L. R. Dragstedt, Chicago, discussed the physiologic principles in surgery of the pancreas. C. B. Huggins, Chicago, described experiments which demonstrated a fibrinolytic factor in prostatic fluid. This enzyme has previously been noted only as a product of bacterial metabolism but it would also seem to be a normal physiologic component of prostatic fluid. H. P. Jenkins and Charles Dunham, Chicago, presented their studies on the irritant properties of catgut tubing fluid and pointed out that "some of the irritant properties attributed in the past to the catgut itself are in reality due to residua of a high boiling point solvent used by the manufacturers in the preparation of catgut, such solvent not being completely removed before final tubing of the catgut." S. M. Moore, New York, discussed femoral hernia.\*

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